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13. ABSTRACT *(Maximum 200 words)*

Study 1. A case-crossover study was conducted in male and female Marine Corps recruits in basic training at Marine Corps Recruit Depot (MCRD), Parris Island, SC to investigate the effects of alternative indices of heat exposure on exertional heat illness (EHI) risk. Weather measurements were obtained for 2,069 cases of EHI identified in this population during 1979-1997. As expected, the risk for developing EHI increased with increasing wet bulb globe temperature (WBGT), which is the standard heat index used by the Marine Corps. EHI risk was found to be associated not only with the WBGT at the time of the event, but by the previous day's average WBGT as well. This result suggests evidence of a cumulative effect of previous day's heat exposure in these Marine recruits at MCRD.

Study 2. A matched case control study was conducted to investigate the effects of fitness and conditioning on EHI risk, as well as to compare the risk factors for mild and severe cases of EHI, as distinguished by core body temperature shortly after the event. Physical fitness, anthropometric and physiological measurements were acquired for 660 EHI cases identified in this population for the period 1988-1996 and matched to 1,723 controls by initial training platoon. For severe cases, BMI and initial run-time did not have independent effects, but instead showed a less-than-additive effect at high levels of each. In contrast, BMI and run-time appeared to have independent effects on risk of mild EHI.

Study 3. A cohort mortality study was carried out among male and female U.S. Army personnel hospitalized for heat illness (HI) at U.S. Army hospitals during 1971-2000. Hospitalization records were obtained for 3,971 cases of HI and 17,233 referent cases of appendicitis (APX). Male and female HI cases had a 40% increased rate of all-cause mortality compared to APX cases. Further examining cause-specific deaths, male cases of HI were at increased risk of death from cardiovascular disease (CVD), ischemic heart disease (IHD), and heat related sites (CVD, liver [non-alcohol] and kidney disease deaths combined) compared to APX cases.

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RISK FACTORS AND MORTALITY IN RELATION TO HEAT ILLNESS SEVERITY

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BACKGROUND

Current military training guidelines are based on a WBGT index ranging from 80 up to 84.9°F (26.7 to 29.4°C) (green flag), with continued exercise permitted, to 90°F (32.2°C) and above (black flag), signaling all activities to be stopped. However, Kark et al (1996) found that a large number of exertional heat illness (EHI) episodes occurred well below the traditional warning flag WBGT (green flag) conditions of 80°F (26.7°C), with a majority of the EHI cases exposed to a WBGT $\geq$ 80°F (26.7°C) on the day before becoming a case. We used existing data from the Marine Corps Recruit Training heat illness records for years 1979 - 1997. Risk factors for heat illness, and factors that predict the severity of heat illness, were identified using these existing data sets.

Evidence from the open literature suggests that severe heat illness may cause irreversible acute damage to the heart, lungs, kidney and liver, which could lead to cardiovascular disease (CVD), ischemic heart disease (IHD), chronic liver or pulmonary disease, and/or renal failure. To investigate this potential cause of pre-mature death, cases of heat illness and appendicitis occurring in the Total Army Injury and Health Outcomes Database (TAIHOD) were followed for a period of 30 years.

This report supports STO T: Physical Status and Exercise Performance in Hot Environments, STO U: Fusion of Warfighter Performance, and STP C: Stress Diagnostics.

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EXECUTIVE SUMMARY

This research consisted of three separate investigations of heat illness in the military. The first two studies used data on exertional heat illness (EHI) among Marine Corps recruits in basic training, while the third was a mortality follow-up study of Army personnel after hospitalization for heat illness.

STUDY 1. A case-crossover study was conducted in male and female Marine Corps recruits in basic training at Marine Corps Recruit Depot (MCRD), Parris Island, SC to investigate the effects of alternative indices of heat exposure on EHI risk. Weather measurements were obtained for 2,069 cases of EHI identified in this population during 1979-1997. In the case-crossover design, cases served as their own controls. As expected, the risk for developing EHI increased with increasing wet bulb globe temperature (WBGT), which is the standard heat index used by the Marine Corps. Exertional heat illness risk was found to be associated not only with the WBGT at the time of the event, but by the previous day's average WBGT as well. This result suggests evidence of a cumulative effect of previous day's heat exposure in these Marine recruits at MCRD. Alternative heat indices were identified, which were somewhat better predictors of EHI risk than was WBGT. These alternative indices appeared to be simpler, as they did not include the black globe temperature. Perhaps the simplest index used only the ambient temperature and the relative humidity, and predicted EHI risk at Parris Island somewhat better than did WBGT.

STUDY 2. A matched case control study was done to investigate the effects of fitness and conditioning on EHI risk, as well as to compare the risk factors for mild and severe cases of EHI, as distinguished by core body temperature shortly after the event. Physical fitness, anthropometric and physiological measurements were acquired for the study, which consisted of 660 EHI cases identified in this population for the period 1988-1996 and matched to 1,723 controls drawn from the same initial training platoons. Initial fitness was evaluated by a timed run, and slower run-times were found to strongly increase the risk of EHI in both male and female recruits. A 7% increase in risk of EHI per kg/m^2 of body mass index (BMI = weight/height^2) was observed for male recruits, while among female recruits, BMI was not found to be an important predictor of EHI risk. When the cases of EHI among males were divided into severe (core body temperature $\geq$ 103.1°F (39.5°C)), and mild (core temperature < 103.1°F (39.5°C)) cases, the best fitting models were somewhat different. For severe cases, BMI and initial run-time did not have independent effects, but instead showed a less-than-additive effect at high levels of each. In contrast, BMI and run-time appeared to have independent effects on risk of mild EHI. Exertional heat illness risk models were also constructed using BMI and a measure of oxygen consumption, theVO_{2max}. An advantage of this approach is that standard prediction equations exist for estimating VO_{2max} from run-time in both men and women. The magnitude of the effect of VO_{2max} on EHI risk was found to be nearly identical in both sexes.

We calculated the absolute risk of EHI for male and female recruits, using models based on tertiles of BMI and quartiles of VO_{2max} (for males) and on quartiles of VO_{2max}

alone (for females). Among males, the risk was 4.8 cases/1000 recruits in the highest risk category (BMI $\geq$ 26 kg/m^2 and VO_{2max} < 40.98 ml/min·kg), while among females, the absolute risk was 8.6cases per 1000 recruits in the highest risk category (VO_{2max} < 32.72 ml/min·kg).

STUDY 3. A cohort mortality study was carried out among male and female U.S. Army personnel hospitalized for heat illness (HI) at U.S. Army hospitals during 1971-2000. Hospitalization records were obtained from the Total Army Injury Hospitalization Outcomes Database (TAIHOD) for 3,971 cases of HI. Because data do not exist on the full cohort of Army personnel, it was necessary to use a reference cause of hospitalization as a comparison group. We used 17,233 referent cases of appendicitis (APX). Vital status of these cases was determined through the National Death Index (NDI), and 115 HI and 585 APX cases were found to have died. Male and female HI cases had a 40% increased rate of all-cause mortality compared to APX cases. Further examining cause-specific deaths, male cases of HI were at increased risk of death from cardiovascular disease (CVD), ischemic heart disease (IHD), and heat related sites (CVD, liver [non-alcohol] and kidney disease deaths combined) compared to APX cases. These results provide preliminary evidence for increased risk of mortality among those who have been hospitalized for heat illness. However, more research needs to be done to rule out alternative explanations for these findings, including confounding by early life risk factors such as obesity, or post-military factors that might be associated with mortality and more common among the HI cases in this cohort of U.S. Army subjects.

CHAPTER 1: GENERAL INTRODUCTION AND OVERVIEW

MILITARY RELEVANCE

The overall objective of this report is to improve the understanding of the risk factors for heat illness during military basic training and to determine whether premature mortality is a consequence of severe heat illness, with the long-term goal of improving guidelines for the prevention of heat illness and sequelae.

The current training guidelines are based on a WBGT index ranging from 80 up to 84.9°F (26.7 to 29.4°C) (green flag), with continued exercise permitted, to 90°F (32.2°C) and above (black flag), signaling all activities to be stopped. However, Kark et al (1996) found that a large number of exertional heat illness (EHI) episodes occurred well below the traditional warning flag WBGT (green flag) conditions of 80°F (26.7°C), with a majority of the EHI cases exposed to a WBGT $\geq$ 80°F (26.7°C) on the day before becoming a case. Furthermore, Ramlow (1990) found mortality to be somewhat correlated with the previous day's average temperature. Do these findings suggest a cumulative exposure effect that continues to the next day of training? If a cumulative effect does in fact exist during hot weather training. Would the wet bulb globe temperature (WBGT) index for 1 or 2 days preceding the incident be a better measure for predicting cases of EHI than current daily average WBGT? Also, are there alternative heat stress indices that better predict EHI than the WBGT?

Anthropometric and conditioning factors such as body mass index (BMI) and physical fitness test (PFT) run-times have been reported to increase rates of EHI (13). Until now, it has not been examined whether these risk factors operate similarly for mild and severe cases of EHI. Do the effects of weight, BMI, PFT run-times, and VO_{2max} on EHI differ by severity level? Also, Gardner et al (1996) found that high BMI categories increased risk of EHI. Is it possible to identify specific subgroups of recruits at higher risk of developing EHI by stratifying on BMI and WBGT established flag conditions?

To answer these questions, we used existing data from the Marine Corps Recruit Training heat illness records. Risk factors for heat illness, and factors that predict the severity of heat illness, were identified using these existing data sets. We also investigated alternative indices of heat exposure that may be more accurate tools for the prevention and prediction of future cases of heat illness occurring during military training and exercise.

Evidence from the open literature suggests that severe heat illness may cause irreversible acute damage to the heart, lungs, kidney and liver, which could lead to cardiovascular disease (CVD), ischemic heart disease (IHD), chronic liver or pulmonary disease, and/or renal failure. In particular, heatstroke is known to cause damage to tissue of the heart, kidney and liver (5-6), (13), (16). Does severe heat illness, as evidenced by a history of hospitalization for heat illness, increase the risk of premature death due to cardiovascular disease, ischemic heart disease, chronic liver disease, or renal failure? To investigate these questions, cases of heat illness and appendicitis

occurring in the Total Army Injury and Health Outcomes database (TAIHOD) database were followed for a period of 30 years. The availability of inpatient data and death registry information provided the opportunity to answer these questions from existing data sources.

BACKGROUND

Heat Illness in the Military

Heat illness in the military has been a persistent problem from ancient Roman armies to today's modern armed forces, resulting in unnecessary morbidity, mortality, and consumption of valuable health resources (31). Heat illness, especially in the form of exercise induced or exertional heat illness (EHI), has been a major issue in the training of military recruits leading to mild types of heat illness such as heat exhaustion to the most severe type of heat illness known as heatstroke. Heatstroke is a life-threatening condition if not treated properly and in a timely manner. This life-threatening form of heat illness reportedly caused 20,000 Egyptian troop deaths during the Six-Day War in 1967 because operational demands delayed emergency medical treatment (29).

Clothing and environmental factors such as high ambient temperatures are major contributors to the development of heat illness because they make it difficult to maintain a thermal balance between the body and the environment. Heat illness results when this thermal balance is not met and storage of heat occurs in an individual.

During the 1950's Dr. David Minard established an index using the wet bulb globe temperature (WBGT) as a decision guide for drill instructors to use to determine appropriate levels of physical activity during periods of warm weather training in US Marines. Even with current heat illness prevention guidelines it has been observed by Kark et al (1996) that a large number of heat cases occur at "safe" levels of the daily WBGT index during physical training.

A number of sequelae are associated with heat illness and are both acute and chronic in nature. Acute sequelae comprise mild to severe cardiovascular and CNS disturbances, i.e., hypotension and fainting, as well as cellular damage involving the brain, kidneys, liver and blood clotting mechanisms (30). It is generally understood that an individual who has suffered a serious heat illness will display reduced tolerance to heat for some undetermined time after an episodic heat illness (68).

There have been a large number of animal and human physiology studies done to understand the relationship between biological mechanisms and environmental factors that lead to heatstroke. However, only a few epidemiology studies to date have examined this problem. The association between heatstroke and premature death has not been studied and could add insight into long-term effects of heatstroke.

Physiology of Heat Illness and Sequelae

Pathophysiology. The human body's reaction to heat stress is controlled through a pathway of neural feedback from the central nervous system (CNS) (23), (63). The hypothalamus monitors the temperature of blood flow integrates and sends thermal messages via neurotransmitters to the appropriate effectors (sweat gland, blood vessels). The anterior portion of the hypothalamus acts as the body's thermostat, integrator, and compiler of messages from the thermoreceptors in the skin, muscles, stomach, and other CNS tissue. The preoptic area of the hypothalamus provides and maintains a reference temperature that activates appropriate neurons responsive to core or deep body temperature and skin temperature. The hypothalamus controls for aberrant temperature extremes and maintains the brain temperature at a safe level through direct activation of physiologic mechanisms such as blood flow and sweating, required to return the reference point to its original level.

Acute Heat Disorders. The human body goes through a number of physiological adjustments to maintain the core temperature within safe limits to preserve life. The blood vessels dilate and heart rate increases to transport warm blood to the skin where heat can be dissipated by radiation and convection (60). Additional heat is dissipated to the environment by the sweat glands releasing water for evaporative cooling. The heat loss by radiation is a direct function of surface temperature (59). The higher the skin temperature, in relation to surfaces and/or air, the more heat is lost through thermal radiation. Heat loss through evaporation becomes important if air temperature is higher than skin temperature. When this occurs, the direction of convection is reversed and the body can gain heat. Evaporative sweating cannot dissipate this build up of heat when there is high heat and high humidity. If this water vapor is collected on the skin as sweat, there is no heat loss to the environment leading to increasing core temperature and inevitable heat illness.

Exertional heat illness (EHI) is comprised of a number of acute heat illness disorders (25). These acute disorders of heat illness include *heatstroke* (ICD-9 code 9920), *heat exhaustion* (ICD-9 code 9923-9925), and *heat cramps* (ICD-9 code 9922).

Classic heatstroke is in most cases associated with prolonged exposure to a hot environment where strenuous exercise is not involved (41), (72), (75). In the United States, it is observed predominately in the elderly who have reduced cardiac output and typically develops from several days of high heat exposure in a non-air-conditioned environment (3), (34), (41). This form of heatstroke has a high mortality because victims frequently have chronic illness and are most likely to be at an advanced stage of chronic illness (54). Classic heatstroke commonly includes an absence of sweating, whereas in exertional heatstroke this is not the case (31). On the continuum, heatstroke is defined either clinically or on the basis of a rectal temperature of $\geq$ 104.9°F (40.5°C) with an outcome of death if 106°F (41.1°C) is reached (54). Environmental and clothing variables are the most common factors that affect heat stress, but other important factors include hydration, acclimatization, age, physical fitness, body fat, gender, body size, diet, previous heat illness, drugs and alcohol (25), (49).

Exertional heatstroke in contrast, is quite prevalent in healthy young adults performing strenuous physical training in warm and humid weather (54). However, classic or sedentary heatstroke is quite rare. Exertional heatstroke usually occurs from continuous or heavy exertion in hot environments (41-42). Onset of exertional heatstroke is sudden occurring during or shortly after physical exertion leading to collapse (with or without syncope), followed by confusion, aggressiveness, dulled sensitivity, or coma (56). This syndrome frequently develops in a matter of minutes with severe organ damage if not treated immediately.

Exertional heat injury is a multisystem disorder involving hyperthermia in combination with organ damage or severe dysfunction (typically metabolic acidosis, acute renal failure, muscle necrosis, or liver necrosis) (56), (12). It is classified as including more-severe symptoms than exertional heat exhaustion, with fewer complications than those of heatstroke (such as acute renal failure) (54). Organ damage or dysfunction is not often evident in the early stages of heat injury, so distinguishing exertional heat injury from heat exhaustion may not be possible (see below) during the first few hours of illness.

Exertional heat exhaustion is a non–life-threatening multisystem, reversible disorder that is caused by the failure of the circulatory system to meet the demands of thermoregulatory, muscular, cutaneous, and visceral blood flow (54). It is a syndrome of dehydration without serious metabolic complications or organ damage (41), (76). Symptoms of heat exhaustion consist of headache, nausea, vertigo, weakness, thirst, and sometimes dizziness. Heat exhaustion is generally thought to produce minor elevations of core temperature -- 100.4 to 102.2°F (38.0 to 39.0°C) (54).

Chronic Heat Disorders. Another area of concern with heatstroke is the later outcome. Once individuals are diagnosed as heatstroke victims, are they more susceptible to other types of illnesses either acute or chronic? Heatstroke is known to cause damage to tissue of the heart, kidney and liver (13), (24), (43), (61). One or more of these systems may be compromised because of "over heating", possibly placing these individuals at higher risk of developing chronic heart, pulmonary, kidney and/or liver diseases that may possibly lead to premature death.

Some long-term chronic effects from exposure to heat stress based on experimental and epidemiologic evidence have been suggested (7), (49-50). Dukes-Dobos (1981) classified possible heat-related chronic health effects into three types: Type I – the after-effects of acute heat illness; Type II - cumulative effects of long-term exposure; and Type III - effects of residence in hot climate. Documented evidence of life-threatening arrhythmia and other serious cardiovascular events have been observed in a population of US Marine recruits at Parris Island, SC (35), (37). Other evidence of ischemic heart disease (IHD), cardiovascular disease, and non-malignant digestive disease has been reported in occupational environments (46), (79).

Heat Balance and Heat Exchange. To understand what makes an individual a heat casualty one needs to understand the concept of "thermal balance". The main approach to thermal balance is the human heat balance equation (49), (62):

$$\Delta S = (M\text{-}W_k) \pm C \pm R \pm E \qquad (1.1)$$

Where the rate of heat storage (affecting internal temperature) of the human body (S) is calculated by the addition and/or subtraction of surface heat exchanges made up of convection (C), radiation (R), evaporation (E) and internal body heat production (M), with the remaining energy being work (W_k). Heat storage is a term that indicates when an individual is at thermal equilibrium with the environment (62). Thermal balance is achieved when S = 0. An individual's body temperature increases with positive heat storage (S) and decreases with negative heat storage.

Convection and radiation are known as dry or "sensible" heat exchange because body surface evaporation is not involved (62). For that reason these exchanges can be measured or sensed as differences in temperature. Evaporation is known as wet or "insensible" heat exchange, since the physical changeover of water to vapor is not directly reflected by a change in temperature.

Thermoregulation. The management of these parameters to maintain a thermal equilibrium is known as thermoregulation (63). Thermoregulation is accomplished by exchange of heat between the body and the surrounding environment. The environmental factors that determine the potential for heat exchange make up the thermal environment (55), (62). These factors are air temperature, air movement (V), humidity (RH) and non-ionizing radiation.

Thermoregulatory heat transfer between the individual and the environment is negatively affected by a combination of factors known as environmental thermal stress (60). The subsequent strain on the body's thermoregulatory mechanisms is determined by a number of physiologic parameters. These parameters are core temperature (T_c), skin temperature (T_{sk}), sweating rate, metabolic rate and heart rate.

Assessing Heat Stress and Strain

A number of methods for measuring the thermal strain that an individual will experience have been devised over the years. These methods include indices that reduce a number of pertinent parameters to a single ordinal measured response. A number of popular methods used are briefly described below.

The effective temperature (ET) is a sensory index of the degree of warmth an individual would perceive with various combinations of air, temperature, humidity and air movement (21), (28), and is expressed in the form.

$$ET = 0.492T_a + 0.19p_a + 6.47 \qquad (1.1)$$

Where T_a = ambient temperature and p_a = ambient water vapor pressure. To find ET, air and wet-bulb temperatures and wind speed are entered into a provided nomogram. The ET scale is widely used, but most appropriate in warm environments, where radiation effects are at a minimum, light clothing is worn, and individuals are sedentary or engage only in light activity (1). Another limitation of the ET is that different climates with the same ET values do not result in the same tolerance times, rectal and skin temperatures, or sweat rates. The "New" Effective Temperature scale (ET*) was developed to address the shortcomings of the ET (6), (22), (26).

$$ET^* = T_o - ((P_a - 0.5 \cdot P_{ET^*}) / (-\Psi/w)) \quad (1.2)$$

Where T_o = operative temperature, P_a = ambient vapor pressure, $0.5 \cdot P_{ET^*}$ = the saturated vapor pressure at ET* in a 50%RH environment, and $-\Psi/w$ = a unique parameter of the sensible to evaporative heat exchange coefficients of the given environment. Additional variables are entered into the calculation of ET* to obtain a more accurate prediction of thermal strain than what the original ET produces.

The Wet-Bulb Globe Temperature (WBGT) index for hot environments was developed for the military to help minimize the occurrence of heat casualties among trainees, but its use has been expanded to include occupational conditions (32), (49). Preventive measures for heat illness using the WBGT were first implemented at Marine Corps Recruit Depot (MCRD) in 1953 (44-45). In the previous two-year period (1952-1953) before the WBGT was introduced the average weekly incidence rate of heat casualties at MCRD during summer months was 39.5 cases per 10,000 (2/3 of all cases of heat illness admitted to sick call in the Navy and Marines). By comparison, with preventive measures based on the WBGT the rate was 12.5 per 10,000 in 1955 and 4.67 per 10,000 in 1956. In fact, the reduced rate of heat casualties in 1956 occurred despite hotter training conditions than the previous year.

The WBGT index is computed from readings of natural wet-bulb (T_{nwb}) and black globe (T_{bg}) temperatures in the absence of a solar load.

$$WBGT = 0.7T_{nwb} + 0.\ 3T_{bg} \quad (1.3)$$

When a solar load is present, air temperature (T_a) is also measured and the formula becomes.

$$WBGT = 0.7T_{nwb} + 0.2T_{bg} + 0.1T_a \quad (1.4)$$

Ceiling WBGT limits recommended by the National Institute for Occupational Safety and Health (NIOSH) for heat-acclimatized individuals are 102°F (38.9°C) for light workload, 98°F (36.7°C) for mild workload, and 95°F ((35°C) for heavy workload (49). These limits were set to help maintain core temperature below 100°F (37.8°C) and assumes that one layer of clothing is being worn.

A 2-hour time weighted average (TWA) is used in industry when a worker is continuously exposed to a hot environment and expressed in the form (1).

$$\text{Ave. WBGT} = \frac{(WBGT_1)*(t_1) + (WBGT_2)*(t_2) + \ldots + (WBGT_n)*(t_n)}{(t_1) + (t_2) + \ldots + (t_n)} \quad (1.5)$$

These heat exposures are 2 hour TWA periods that an individual works on a shift including time spent in the heat and while on break.

Heat Illness in U.S. Marine Recruit Training

Marine Recruit Training. U.S. Marine recruit training has caused many heat illnesses and, as a result, has produced the most extensive research on the problem. The current standard operating procedures and uniform training schedules for basic training were implemented in 1976 (46). Recruit basic training is conducted at the Marine Corps Recruit Depot, Parris Island (MCRD-PI), SC, for all male recruits in the eastern half of the United States and all female recruits nationwide and lasts for 12 weeks. This 12-week period is comprised of three phases (basic learning, marksmanship and field training), which includes 10-11 weeks of formal training and 1 week of informal training at the halfway point.

The majority of training days begin with 2 hours of physical exercise that includes a 1-3 mile run 3 days per week for male recruits and a 1.5-mile run for females. Their 2 hours of physical exercise are scheduled between the hours of 7 am to 9 am during the months of May thru September so that the more strenuous activity of physical exercise can be done in the milder temperatures of early morning. However, before formal training can begin all new recruits must pass an initial physical test consisting of pull-ups, sit-ups, and a 1.5-mile run for men or a .75-mile run for women. Phase-1 training with duration of four weeks consists of intense physical conditioning and mental discipline, which includes calisthenics, obstacle courses, sprints, marches, and runs. Phase-2 training takes place during weeks 5 through 8, and is dedicated to marksmanship, combat skills, field training, and continued physical conditioning. For the last four weeks, phase-3 completes training and prepares the recruits for graduation as United States Marines.

Prevention Measures. Heat illness prevention guidelines were first implemented during World War II as a consequence of 200 Marine Corps deaths during basic training (10), (41), (62). Clinical studies of recruits conducted at Parris Island during the 1950's lead Belding, Minard and Yaglou to develop the wet bulb globe thermometer (WBGT) index to assess heat stress in a semi-tropical climate (9), (44-45), (80). These studies found that most heat illness cases at Parris Island occurred with strenuous exercise when the WBGT was 80°F (26.7°C) or higher. More than half of the heat illness cases during the 1950's occurred during daytime infantry drill and training marches (43). Further studies confirmed that heat illness rates were reduced by decreasing the level of exercise, increasing rest periods and hydration, and reducing the use of heavy impermeable clothing as the WBGT rose above 80°F (26.7°C) (44), (51-53). These findings were applied to developing a standard guideline to minimize heat illness using

four categories of high WBGT (green flag = 80-84.9°F (26.7-29.4°C); yellow flag = 85-87.9°F (29.4-31.1°C); red flag = 88-89.8°F (31.1-32.2°C); and black flag = 90°F (32.2°C) or higher. For example, exercise continues with caution during green flag, strenuous exercise (e.g.," marching at normal cadence") ceases immediately for phase 1 recruits during yellow flag, strenuous exercise is shortened for all recruits during red flag, and all outdoor physical training is suspended during black flag conditions (12), (77). As a result of these regulations, strenuous exercise is now done during the cooler temperatures of early morning hours.

For the past 30 years command policy has enforced mandatory hot season regulations, which include guidelines for heat casualty prevention, management, and surveillance. Important features of these guidelines include protocols for regulation of clothing, exercise, and rest periods based on the WBGT index, and a strict water schedule of about 1 liter per hour while exercising depending on WBGT category (16).

Treatment of Cases. At MCRD-PI treatment of heat cases is administered by medical corpsmen in the field and US Navy physicians and nurses at the local clinic and naval hospital. Ice, fluids and motor transport must be available during all strenuous physical exercise (36). When a recruit presents signs of heat illness, standard procedures require immediate action by measuring rectal temperature, cooling with ice-water as needed, and transportation to the Parris Island Branch Medical Clinic located within 10 minutes from any point on the island by motor vehicle. The clinic has a heat casualty "cold room" equipped with ice-water baths, electronic rectal temperature monitors, intravenous fluids and resuscitation equipment. All severe heat illness cases are then transferred to the Beaufort Naval Hospital for further evaluation and treatment.

Epidemiology of Heat Illness

Studies of EHI Among Marine Recruits. Exertional heat illness is a constant problem in military training, resulting in training ineffectiveness and loss of personnel. A number of epidemiologic studies have been done to look at exertional heat illness (EHI) incidence and risk factors among Marine recruits during basic training in hot weather. Epidemiologic methods were applied to data collected on heat illness cases for years 1979 to 1991 at the MCRD-PI to identify suspected risk factors (25), (36).

A preliminary descriptive study was done to examine the incidence rate of EHI stratified by weather conditions, gender and hospitalization (36). All EHI cases occurring among 217,000 Marine Corps recruits entering 12-week basic training at Parris Island, SC during 1982-1991 were collected from hospital and clinic records. This study consisted of 1454 cases, 89% males and 11% female. Most of the cases (88%) occurred during May through September with the majority of the cases occurring during the cooler morning hours when the recruits performed strenuous exercise. Eleven percent of male cases and no female cases were hospitalized. Even well below flag conditions of $\geq$ 80°F (26.7°C), heat casualties were observed at WBGT levels as low as 65°F (18.3°C), but the rate of heat casualties increased noticeably between the hours of 7 am to 9 am as the wet bulb globe temperature index (WBGT) increased. The EHI rate was found to have a 26-fold increase at WBGT of 75°F (23.9°C) to < 80°F

(26.7°C), compared to baseline heat illness rates at < 65°F (18.3°C), for immediate day exposures. While the EHI rate showed a 39-fold increase at WBGT of 75°F (23.9°C) to < 80°F (26.7°C), compared to baseline EHI rates at < 65°F (18.3°C), for previous day exposures. Exposure to a WBGT of > 80°F (26.7°C) was uncommon (25%) among the early morning heat illness cases, while 87% of heat illness cases had previous day WBGT readings above 80°F (26.7°C), pointing to a possible cumulative effect of heat exposure. Kark et al concluded that risk for EHI in military training increases as WBGT levels rise above 65°F (18.3°C), primarily with strenuous exercise (e.g., running); and recommend that heat stress exposure on prior days needed further study.

A matched population-based case-control study was conducted on a subgroup of the same Marine recruit EHI case cohort previously described (1988-1992) (23). Physical fitness and anthropometric measurements were obtained for 391 of 528 male cases of EHI identified in this population of Marine recruits and for 1467 of 1725 male controls matched to cases by initial training platoon (25). Gardner et al. found that the risk for developing EHI increased with body mass index (BMI = weight /height^2), as measured at onset of basic training, and with time required by the individual recruit for completing a 1.5-mile run. Gardner reported that recruits with a BMI of $\geq$ 22 kg/m^2 and a 1.5 mile run-time of $\geq$ 12 minutes had an 8-fold higher risk for developing EHI during basic training when compared with those recruits with BMI less than 22 kg/m^2 and 1.5 mile run-time under 10 min ($p < .001$). Only one-fifth (18%) of male recruits fit these conditions for high risk, but they represented almost half (47%) of the EHI cases that occurred during the 12-weeks of basic training. From these findings it was suggested that this identified high risk group may benefit from effective intervention measures such as training during the cooler months or going through a slower conditioning schedule if cool weather training is not an option.

Kark et al did a population based study to examine the association between EHI and serious arrhythmia (35). Records of all deaths, life-threatening arrhythmias, and military cadre at MCRD-PI were reviewed for the years 1979-1990. They found that the incidence of life-threatening exertional arrhythmia in the study cohort was 3/216 persons with exertional heatstroke (within 5 min of onset) and 4/267,333 persons without exertional heat illness (EHI). Exertional heatstroke accounted for more than half the episodes of unexplained life-threatening arrhythmia in the study cohort with a RR = 928 ($p < .000001$). This evidence suggests elevated risk of acute cardiovascular injury from exertional heat stroke and provides a basis for following a heat illness patient cohort to determine possible chronic outcomes (18).

A recent follow-up study based on the same Marine recruit dataset was used to evaluate long-term re-occurrence of more severe EHI in military recruits who experienced EHI during basic training (57). Cases were identified as those recruits who completed at least 6 months of military service and had EHI recorded as an outpatient (N = 872) or inpatient (N = 50) during basic training in 1979-1991 at the MCRD-PI. They were compared to 1391 controls that did not experience EHI during basic training. These subjects were followed from 6 months after appointment into the military through the following 4 years of military service. Military retention was determined through

military personal records and additional hospitalizations were found through hospital databases. For recruits who experienced EHI during basic training, military retention rates were slightly lower compared to those recruits who did not (24% vs 30% at 4 years). The investigators found that outpatient EHI cases initially had about 40% higher subsequent hospitalization rates compared to noncases, yet these differences declined over time and analysis revealed little relationship to EHI. EHI cases were also observed to have higher rates of subsequent hospitalizations for EHI, but the number of cases was too small to provide stable comparisons. Phinney et al (2001) concluded that hospitalization for EHI is uncommon during continued military service after an initial episode of EHI during basic training, and that occurrence of EHI during basic training has only a small effect on additional military retention and hospitalization.

Occupational Studies. A small number of epidemiology studies have been done to look at EHI risk factors in an occupational setting. Most of the earlier studies concentrated on acute and chronic heat exposure and mortality (50).

A case-control study of miners was done to identify the risk of heat exhaustion at a deep underground metalliferous mine in Australia in relation to the body mass index (BMI) and predicted maximal oxygen uptake (VO_{2max}) (17). Cases were identified as a miner in one of two underground mines operating between 1200 and 1800 meter depth and having a significant history of heat exhaustion during October 1, 1997 to September 30,1998. Controls were identified as miners in these same underground mines who had a periodic health assessment and health surveillance during the study period and did not have an episode of heat exhaustion. The 65 acute heat exhaustion cases had a significantly ($p = 0.006$) higher BMI than the 119 controls. Risk of heat exhaustion was significantly greater for cases with a BMI of 32 to 37 kg/m^2, compared to controls with a BMI of less than 27 kg/m^2 (OR = 3.63; 95% CI, 1.42-9.36). It was also reported that heat exhaustion risk increased with decreasing VO_{2max} (OR = 1.85; 95% CI, 0.75-4.59). Donoghue et al (2000) recommended that deep underground miners should try to maintain a BMI of 24 to 27 kg/m^2, but the selection of miners on the basis of BMI should not be used as a substitute for engineering controls such as ventilation and refrigeration.

A second study examined cardiovascular disease mortality among potash miners exposed to heat (79). The study cohort was comprised of all male workers at a potash mine in France identified through personnel files as of January 1, 1977 and were followed until December 31, 1987. Workers with less than three years of employment were excluded. The cohort consisted of 4,484 miners exposed to the underground potash mine environment and 3,714 miners who were not exposed (above ground). Wild et al (1995) found that mortality from ischemic heart disease (IHD) was higher for underground workers when compared to daylight workers (RR = 1.6). The investigators also found that mortality from IHD *decreased* as exposure (years underground) increased over time (SMR 3.67 to SMR = 1.48) for exposures > 20 years and exposures $\geq$ 20 years. This inverse trend may represent an example of a healthy worker survivor effect. This overall increase in mortality from IHD may have to do with heat-related

acute cardiovascular injury as reported by previous studies (35), (37), although other mining hazards cannot be ruled out.

Another study looked at fatal work related injuries of steelworkers in a nested case-control design, which included a retrospective cohort of men employed in a steel plant of USIMINAS, Brazil, between January 1977 and August 1990, who were followed to November 1992 (7). The cases were defined as all workers in the cohort who died from a work injury during the study period and whose notification of death was sent to the Brazilian Ministry of Labour. Four controls per case, matched to cases on year of birth, were randomly selected from among workers employed in the plant at the time of death of the matching case. Data on potential risk factors for occupational injury were collected from company records. For the controls, risk data were collected for the period preceding the death of the matching case. There was a total of 37 work related deaths during the study period and complete personnel records were available for 140 controls. Risk of fatal injury at work was significantly ($p < 0.001$) associated with exposure to heat, for both high heat intensity (Adjusted OR = 6.80; 95% CI, 2.13 to 21.65) and mild intensity (OR = 2.89; 95% CI, 0.92 to 9.07). Barreto et al (1997) also calculated a hazard score, which was a combined measure of noise, heat, dust, and gas exposure and ranged from 1 to 5. They found hazard score to be a significant ($p < 0.001$) predictor for fatal injury. More importantly for this research, heat exposure appeared to be a strong predictor of fatal injury with a highly significant trend as intensity increased (χ^2 trend, $p < 0.001$) independent of the other occupational hazards.

An earlier longitudinal study of 59,414 steelworkers employed at seven plants in Allegheny County, PA from 1953 to 1970, examined possible relationships between long-term heat stress and cause- specific deaths (50). The investigators identified jobs that they observed to involve heat stress exposure. A pre-selected list of "hot jobs" was evaluated to estimate the environmental and metabolic heat load of the workers, which was used to form a category index of heat stress exposure represented by the wet bulb globe thermometer (WBGT) index. The control population consisted of workers from the same cohort who never held a position in a heat-related job. Redmond et al found an increased risk of death from cardiovascular disease (RR = 2.96, $p < 0.05$) for workers with less than 6 months of exposure and a downward trend in mortality for workers who remained on the job, indicating a possible relationship between the inability to work in jobs involving heat stress and health status. This downward trend in mortality is probably due to a healthy worker effect since sick workers had a tendency to leave jobs with high heat exposure as a result of their cardiovascular condition. The investigators also found an increased risk of nonmalignant digestive disease (excluding cirrhosis) mortality (RR = 3.48, RR = 2.75, $p < 0.05$) for steelworkers exposed to WBGT levels > 79°F (26.1°C) and > 82°F (27.8°C) of environmental heat for > 15 years. The investigators could not explain this finding, although exposure to toxic solutions or gaseous fumes from molten metals could not be ruled out. Excess elevated levels of lipopolysaccaride (LPS) are known to occur during heatstroke from major damage to the intestinal gut wall (27). This excess of LPS may overwhelm the liver's binding and detoxifying capacity resulting in a potential of toxic LPS entering into the systemic blood circulation, which could lead to shock or possible death (27).

Heat Wave Studies. A majority of the heat wave studies conducted over the last 20 years have dealt with heat exposure in relation to mortality on an elderly population during summer time heat waves. A case in point is the record-setting heat wave that hit Chicago during July of 1995 when approximately 700 excess deaths occurred. A matched case-control study of this episode was conducted to identify risk factors associated with heat-related death and death from cardiovascular causes from July 14 thru July 17, 1995 (66). Three hundred and thirty nine cases were identified through death certificates as persons older than 24 years of age in which one of three potentially heat-related causes was listed: either heat was listed as the primary cause of death, with no cardiovascular disease; cardiovascular disease was listed as the underlying cause of death, with no heat exposure; or cardiovascular disease was listed as the primary cause of death and heat as a contributing cause. One control per case was selected, matched by age and place of residence. Risk of heat-related death was higher for people with existing medical problems and confined to bed (OR = 5.5; 95% CI, 2.5-12.1) or unable to care for themselves (OR = 4.1; 95% CI, 2.0-8.5). Also at increased risk were those who stayed at home (OR = 6.7; 95% CI, 3.0-15.0), were living alone (OR = 2.3; 95% CI, 1.5-3.6), or for whom residence was on a top floor (OR = 4.7; 95% CI, 1.7-12.8). In a multivariate analysis, the strongest predictors for heat-related death were again being confined to bed (OR = 8.2; 95% CI, 3.1-22.0) and living alone (OR = 2.3; 95% CI, 1.2-4.4). Deaths classified as due to cardiovascular causes had risk factors similar to those for heat-related death. Differences in age did not appear important, possibly due to the sample size of the study or because only two age strata were defined as above or below 76 years. Thus, those at greatest risk of death from the heat were people with medical illnesses who were socially isolated.

One of the few epidemiology studies having made reference to a possible cumulative effect of prior day temperature on mortality was conducted by Ramlow (1990). These authors studied total mortality using a retrospective cohort design after a heat wave occurred during the summer of 1988 in Allegheny County, PA, with daily maximum temperatures near or above 90°F on 15 consecutive days (59). During that period there were a total of 697 deaths from all causes in the county, compared with an expected 587 deaths (SMR = 1.19, $p < 0.01$). The daily mortality was observed to be somewhat correlated with the previous day's average temperature ($r = 0.49$, $p < 0.01$), suggesting a cumulative effect of continuous high daytime and nighttime temperatures on mortality.

Jones and colleagues examined morbidity and mortality that occurred during the 1980 heat wave in St Louis and Kansas City, Missouri. A retrospective cohort study was used to assess the association between morbidity and mortality, and heat exposure. Heat-related illness and deaths were identified in the two cities from death certificates, medical examiners' records, and hospital and emergency room records (34). Non-heat wave data from July 1978 and 1979 were used for comparison to heat wave data from the July 1980 heat wave. Deaths from all causes were observed to have increased by 57% and 67% in St Louis and Kansas City compared to only a 10% increase in rural areas of the state where temperatures were lower (heat-island effect).

Incidence rates of heatstroke, defined as severe heat illness with a documented ante-mortem or post-mortem body temperature of $\geq$ 106 °F (41.1°C), were 26.5 and 17.6 per 100,000 in July 1980 for St Louis and Kansas City. Heatstroke rates were 3.4 and 2.1 per 100,000 for St Louis and Kansas City, respectively, for those persons aged 19 to 44. The ratios of age-adjusted heatstroke rates were approximately 3 to 1 for nonwhite vs white persons and about 6 to1 for low vs high socioeconomic status. The observed difference in race most likely was a result of confounding from socioeconomic status due to the fact that lower income groups, comprised of a large black population did not have access to air conditioning.

Another study based on the data collected for the previous St Louis and Kansas City area retrospective cohort study was used to identify risk factors associated with heatstroke by way of a case-control design (40). The investigators collected questionnaire data on 156 cases with heatstroke (severe heat illness with documented hyperthermia) and 462 control subjects matched on age, sex, and neighborhood of residence. Risk factors associated with heatstroke were identified using a stepwise logistic regression (40). Alcoholism (RR = 15.02; 95% CI, 1.87-120.43) and residence on higher floors of multistory buildings (RR = 1.59; 95% CI, 1.24-2.03) were found to be associated with increased risk of heatstroke.

It appears that people who were exposed to summer "heat waves" were at a higher risk of death than those who were not. Some risk factors identified were current medical conditions, residence on higher floors of multistory buildings and non-access to air-conditioning. Daily mortality was found to be somewhat correlated with previous day's average temperature, suggesting a cumulative effect of previous day's heat exposure.

Risk Factors for EHI and Heatstroke

A number of risk factors have been identified for EHI and heatstroke, primarily in the domain of weather, physical conditioning and acclimatization (4), (14), (25), (53). Anthropometric and environmental factors such as BMI and the WBGT temperature have been reported to increase rates of heat illness.

Poor physical condition is a risk factor for EHI (4), (38), (69). Weather conditions also present critical risk factors for EHI. As noted above, the early recruit studies established that most heat illness cases at Parris Island occurred with strenuous exercise when the WBGT was 80°F (26.7°C) or higher (36), (44). In the 1950s, more than half of heat illness cases occurred during daytime infantry drill and training marches (45). Further studies demonstrated that as the WBGT rose above 80°F (26.7°C), heat illness rates were reduced by limiting the level of exercise, increasing rest periods, increasing hydration, and reducing heat-retaining clothing (10). The established flag conditions used for regulating training activities by WBGT were intended for marching, rather than running, while the focus of physical training in recent years has been more on middle-distance running (1–3 miles) than marching (12). Marching with a heavy load generates about 500 Watts of heat, whereas running at 8 to 10 mph generates 1,000 to 1,200 Watts (9), (75). This increase in higher metabolic-rate

from more intense training activities leads one to expect that during high physical activity periods EHI casualties occur at lower WBGT levels than would normally occur with marching. This was shown in the study by Kark et al (1996), described above, in which they observed an increased risk for EHI at WBGT levels as low as 65°F (18.3°C).

Acclimatization increases the efficiency for heat dissipation, but its benefits can be decreased or cancelled out by infection, dehydration, salt depletion, loss of sleep, or the use of drugs or alcohol (64), (74). Alcohol consumption has been found to increase the risk of heat illness, since alcohol is known to cause dehydration and as a result reduce sweating, an important pathway to reduce heat through evaporation. Acclimatization reduces the risk for EHI by increasing the sweat rate, decreasing the sodium content of sweat, and initiating sweating at a lower body core temperature (18), (47), (78).

Pre-existing health conditions and medications can place an individual at high risk for developing heat illness (8), (37). Health conditions that can make adjustment to hot environments more difficult include prior history of heatstroke, pregnancy, obesity, skin disorders, sunburn, and poor hygiene (e.g., dirt that occludes sweat gland openings). Medications, caffeine, loss of sleep, and missed meals can also predispose an individual to EHI (73-74). Acute illness, especially infection, restricts the body from producing sweat, eliminating a major pathway of heat transfer from one's body to the environment (42), (64). Chronic diseases such as cardiovascular disease decrease the efficiency of flow of blood from the internal organs to the surface of the skin where convection takes place inhibiting the transfer of heat from the body to the environment increasing core temperature in the interim.

The period of increased risk for repeated episodes of EHI is not known. However, Kark reported that approximately 10% of cases among Marine Corps recruits at Parris Island had more than one episode of EHI during their 12 weeks of basic training (36). Continual risk has been mentioned in the literature most often with exertional heatstroke. A number of physiological studies on the effects of repeated exposures to exertional heat stress suggest that there may be an increased vulnerability for several months following exertional heatstroke (5), (67), (70). The only known epidemiologic study on this topic did not support this hypothesis, however. A recent study at MCRD-PI designed to evaluate the risk of recurrent EHI failed to find evidence that EHI cases were more likely than others to suffer from additional heat illnesses (57). More studies are needed to properly address this issue, examining the effect of severe EHI and heatstroke on recurrent heat injury.

Risk Factors for Premature Mortality Following Severe Heat Illness

Under hot conditions there is inefficient heat dissipation, and blood flow to the skin increases requiring a large rise in cardiac output (60). As body temperature increases, more blood flows to the skin for heat dissipation. These circulatory demands of continued physical activity and heat stress may also impose on visceral blood flow to the point of producing organ dysfunction or cellular injury (71). As strenuous physical activity produces more body heat than can be effectively released into the environment, core temperature continues to increase, sweating reaches maximum rates, and dehydration increases, complicating the cardiovascular and metabolic stresses of physical activity and thermoregulation (15), (49), (58). These stresses at their extreme levels may combine to produce cardiovascular collapse, acute renal failure, adult respiratory distress syndrome (ARDS) and/or liver damage (19-20), (52), (67). Heatstroke is known to cause a number of conditions as a result of its effects on various organ systems of the human body. As noted earlier, heat, especially during strenuous physical activity, places extreme demands on the cardiovascular system. When the cardiovascular system is stressed past its capabilities then cardiovascular collapse (shock or a fall in blood pressure) becomes a problem in the early stages of exertional heatstroke (39), (42), (43). The role of cardiac arrhythmia is uncertain, although a number of cases have been documented (35), (39).

Kark et al reviewed all EHI cases, serious cardiovascular events and deaths among 269,000 recruits in Marine Corps training at MCRD-PI during a 12-year period. There were 7 life-threatening cardiovascular events (5%) among 137 patients suffering from exertional heatstroke versus 4 (0.0015%) among 267,500 recruits without EHI (26). The author concluded that risk of life-threatening cardiovascular events during exertional heatstroke was at least 3,000 times higher than exercise without EHI. Exertional heatstroke accounted for 7 of 11 fatal or serious sudden cardiovascular events in this population.

The previous findings from the literature suggest that heatstroke may cause irreversible acute damage to the heart, lungs, kidney and liver, which may compromise thermoregulation. If heat balance cannot be maintained because of this irreversible acute damage, then these organ systems could be overwhelmed over time and lead to chronic disorders that might result in an increased risk of premature death when exposed to moderate and high heat conditions.

Wild and Redmond also reported cardiovascular events in their results from occupational studies described previously. Wild found that mortality from ischemic heart disease (IHD) was higher for underground workers exposed to extreme heat. Redmond observed a significant increased risk of death from cardiovascular disease for workers, although the risk was present among those with less than 6 months of heat exposure. Those two studies suggest a possible relationship between cumulative heat exposure and its effects on the cardiovascular system leading to death. However, it is not known if these cardiovascular conditions existed before these workers were exposed to heat.

Redmond also found an increased risk of nonmalignant digestive disease mortality for steelworkers exposed to high levels of environmental heat for > 15 years. This could point to a possible association between continuous high heat exposure and serious digestive system injury.

USARIEM Studies

The following chapters describe individual studies that explore some of the questions raised in this literature review. Chapter 2 investigates alternative heat indices to the current heat index measure (WBGT) used to measure hot conditions during training at MCRD-PI and whether cumulative daily average WBGT (over 1 or 2 preceding days) is a better measure for predicting cases of EHI than current daily average WBGT. Chapter 3 identifies risk factors in a cohort of Marine recruits that predict both the incidence and the severity of EHI during basic training at Marine Corps Recruit Depot, Parris Island, SC. Chapter 4 examines mortality outcome over a 30-year period in a cohort of U.S. Army soldiers hospitalized for heat illness. The last chapter (chapter 5) summarizes the results and findings of the three investigations with recommendations and questions for future study.

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CHAPTER 2: PARRIS ISLAND STUDY ON WBGT INDICES

INTRODUCTION

Heat illness prevention guidelines based on the hourly wet bulb globe thermometer (WBGT) index, as mentioned in Chapter 1, were first implemented during the 1950's as a consequence of the high rates of heat illness that occurred during basic training at Marine Corps Recruit Depot, Parris Island, SC. These guidelines were founded on clinical research studies, which date back to that time and are still the current standard used in the U.S. military today. The current guidelines are based on a WBGT index range from 80 up to 84.99°F (26.7 to 29.4°C) (green flag), with continued exercise permitted, to 90°F (32.2°C) and above (black flag), signaling all activities to be stopped. However, Kark et al (1996) found that present day's WBGT at the time of exertional heat illness (EHI) episode to be well below the traditional warning flag WBGT (green flag) conditions of 80°F (26.7°C). Of note, a majority of the EHI cases were exposed to a WBGT $\geq$ 80°F (26.7°C) on the day before becoming a case. These findings suggest a cumulative exposure effect that continues to the next day of training. Therefore, the objective of this study was to determine whether the daily average WBGT index for 1 or 2 days preceding the incident is a better measure for predicting cases of EHI than current daily average WBGT. The secondary goal was to investigate the components of the WBGT that where most strongly predictive of heat illness.

A case-crossover design was applied to observe the overall cumulative effect of heat exposure, as measured by the wet bulb globe temperature (WBGT) index, using US Marine recruit EHI cases as their own controls and peak WBGT data on the days preceding case events. Alternative indices of heat exposure were computed from component variables of air temperature (T_a), percent relative humidity (%RH), and solar radiation, measured by black globe temperature (T_{bg}) individually and in combination.

The case-crossover design is used to study the transient effects of intermittent exposure on the risk of acute events in close temporal proximity to exposure (13), (15). This design is essentially a special type of case-control study in which each case is his/her own control. Exposures for each case during an "at risk" or hazard period are compared with the distribution of exposure for follow-up times that occur before and after the hazard period and do not result in an event. The choice of the hazard period follows an analogous approach to air pollution time-series studies in which the hazard or index day is the day of the event or some previous period appropriate to the expected lag or a cumulation between exposure and event (12). The comparison period needs to be chosen carefully since selection bias and confounding can arise from multiple competing biases such as long-term time trends, seasonal patterns, autocorrelation in exposures, and day of week effects (3), (7). This study design requires no additional control subjects to be sampled and can control individual susceptibility by making comparisons within subject. Therefore, this design can control for measured and unmeasured time-invariant potential confounders. This type of study also controls for likely confounding variables such as season trends, day of the week, changes in population size and composition by design instead of by statistical modeling.

METHODS

Study Population

All U.S. Marine Recruit exertional heat illness cases (EHI) were included if they occurred during basic training at the Marine Corps Recruit Depot, Paris Island, SC from 1979 to 1997. Cases were defined as those recruits in basic training who made an emergency room hospital or clinic visit for exercise-induced heat illness, defined as heatstroke, heat injury, heat exhaustion, heat cramps, exertional dehydration, and/or rhabdomyolysis (10). Cases were identified through the Navy medical surveillance system at MRCD-PI with use of the NAVMED 6500 form in addition to hospital and clinic records. Cases were excluded when a WBGT temperature was not available at the approximate hour of EHI episode. (See 2.2.3. "Exposure and other covariates" for source of temperature data.)

Cases served as their own controls defined by reference days excluding an appropriate lag period before and after EHI case-day. The period from which control days were chosen was defined in the following way. Two symmetrical periods, one before and one after each case-day, were defined by determining: 1) a "black out period" around the case-day during which control days would not be chosen; and 2) an outer limit of the control period – i.e., the maximum number of days away from the case-day that a control day could be.

The Blackout Period. The reason that an exclusion or blackout period was necessary was to avoid sampling reference periods that were highly autocorrelated with exposure in the hazard period. Confounding by temperature trends could occur if comparison periods were too close to the event period (7), (12). Choosing referents too close in proximity to the case event is analogous to overmatching in a conventional case-control study (12). The goal here was to select an appropriate blackout period that would control for heat wave effects on WBGT exposures. It was posited that a blackout period of at least 6 to 7 days was needed to eliminate possible confounding by effects of heat wave trends in this study. This a priori estimate was based on previous methodology used in prior air pollution case-crossover studies in which an exclusion period of 6 to7 days was selected. These studies showed that control of confounding by seasonal and long-term time trends was maximized by using shorter lag times, such as 6 days (2). When control periods were separated from the outcome by at least 7 days, the size of variation in WBGT in the matched sets was smaller, allowing for better control of weather patterns such as heat waves. Furthermore, restricting the referent-sampling window to require a 6-day autocorrelation interval between exposures was found to ensure independence among observations by preventing overlap of control and hazard periods and, more importantly, to control for day of the week effects (12).

The following procedures were used to define the blackout period. A working dataset, which included exertional heat illness cases (EHI) and hourly wet bulb globe thermometer index value, was created by merging EHI case and Parris Island weather datasets by year, month, day and hour. This produced an EHI case-weather dataset for years 1979 through 1997 that could be used to examine appropriate blackout periods.

The case-weather dataset was used to create another dataset containing daily mean WBGT values, restricted to the months of June through August and the hours of 10 am to 4 pm to represent peak WBGT temperatures experienced by recruits during summer training. These months were chosen to represent months that would most likely contain the hottest days of summer, as well as the longest duration of hot days. The analyses to this point were done using the Statistical Analysis System (SAS) (16). The dataset consisting of WBGT mean values was then exported to Statistica (17) where autocorrelation was used to compare mean case-day WBGT to mean day WBGT with lags of 1 to 30 days from case-day event. Autocorrelation was highest on adjacent days, as expected. As the number of lag days increased, the autocorrelations between daily WBGT decreased, as one would expect. By about day 5 or 6, the correlation was below 0.3, and it continued to fall fairly steadily until the length of lag increased up to a month. Since the curve tapered off substantially at about 7 days ($r < 0.22$), the decision was made to use a blackout period of one week before or after the EHI case event. This blackout period was two days longer than our original a priori estimate described above.

The Outer Limit of the Control Period. Once the blackout period was selected, a control period could be chosen. Since the end of the blackout period was determined to be 7 days after a case event, the beginning of the control period could start 8 days before or after the case event. To avoid any confounding by a seasonal trend the length of the control period could not continue indefinitely. It has been shown that the symmetric-bi-directional (SBI) case-crossover design controls for seasonal trends in exposure and outcome regardless of the nature of the time trend or the length of follow-up (3). However, by selecting shorter control periods regardless of the nature of the pattern, in this case weather patterns, control of confounding could be maximized from season and long-term time trends. The objective here was to select an outer limit of the control period that excluded any effects of a seasonal trend. It was originally posited that the outer limit of the control period had to be no more than 14 days to avoid a seasonal effect. This estimate was a starting point based on a previous case-crossover air pollution mortality study that found a seasonal trend after 14 days (11). This seasonal trend was possibly due to changes in weather pattern but would be examined more closely in the data analysis stage of our study.

The same SAS dataset containing EHI cases and hourly WBGT temperatures was used as a starting point to create a dataset that could be used for individual regression analyses to determine seasonal trends. The outer limit of the control period was chosen to be close enough to the case day that no important seasonal trends would occur when comparing a day in the control period to the case day. We therefore regressed mean daily WBGT on an indicator for number of days before or after case day. This dataset was restricted to the months of May through October and included the mean daily WBGT for the hours of 7 am to 4 pm. These analyses were extended to the months of May through October so that other cooler seasons could be included to determine a possible seasonal effect in the dataset. A series of regression models were fit, including increasing numbers of days before or after case day. For example, single regressions were developed to compare WBGT on case-day to 1, 2, 3... days after

case-day, and a second regression to compare WBGT on case-day to 1, 2, 3... days before case-day. Twenty-six separate regression equations in all were run, covering increasing of amounts of time from 5 to 120 days before and after EHI case events. These regression models were used to establish how long the reference interval could be extended until an effect of season would be encountered. The steeper the slope ($\beta < -1$), the greater the probability of confounding from a seasonal temperature effect. As expected, the results showed a steady decrease in WBGT as one moves away (before and after) case day. It was decided to limit the control period so that the trend over the period was within one degree Farenheit. Correlated with an outer limit of control period of 21 days before ($\beta = -0.60$) and after ($\beta = -0.78$) the case event. Thus the final period within which control days could be selected included days 8 to 21 before and 8 to 21 after the case event.

Once the blackout period and outer limit of the control period were defined, a number between 8 and 21 was randomly chosen for each case, and their 2 control days were assigned to each case. Control days were selected using a program developed in Agilent Visual Engineering Environment (VEE) to accomplish this process (1).

Selecting the Optimum Exposure Metric. There are a number of approaches available for selecting exposure indicators. Two of these are the "maximum estimate" and "goodness-of-fit" criterion (14). In the first approach, exposure indicators are selected that maximize the observed association (odds ratio) of exposure and disease. This approach has been supported on the basis that an improperly selected indicator of exposure can misclassify exposure in relation to an optimum exposure. This strategy is only reliable with simple regressions that have random, nondifferential error in the single predictor variable or in the case of single 2 x 2 tables with nondifferential exposure misclassification. When measurement error is systematic or confounders are measured with error, the maximum estimate criterion is not appropriate.

Another approach is to select the exposure indicator that maximizes the goodness-of-fit of a statistical model (best fit) to a set of collected data. This was the strategy used to determine the optimum exposure metric for WBGT. We compared the deviance between individual logistic regression models to decide which exposure metric is best (8). The model with the least amount of deviance was the criterion used to select the best model to measure risk for EHI in this cohort of Marine recruits.

Outcome Variables

The outcome studied was exertional heat illness (EHI) defined by incidence of *heatstroke* (ICD-9 code 9920), *heat exhaustion* (ICD-9 code 9924-9925), or *heat cramps* (ICD-9 code 9922).

Exposure and Other Covariates

The measures of exposure were WBGT temperature on the case or reference day, previous daily average WBGT temperature, previous 2-day average of maximum day WBGT temperature, previous peak day WBGT temperature and 2-day peak WBGT

temperature prior to case episode (i.e., 2 days leading up to the case). Previous day WBGT, previous 2-day daily average maximum WBGT, previous peak day WBGT and previous 2-day peak WBGT temperature were also treated as covariates to episode WBGT temperature. Seasonal trend was a potential confounder and was eliminated by study design as described above. WBGT temperature was measured every hour each day during training periods at the Marine Corps Air Station, Beaufort, SC. Individual recordings of hourly WBGT, air temperature (T_a), wet bulb temperature (T_{wb}), black globe temperature (T_{bg}), percent relative humidity (%RH), wind speed and cloud cover by year, month and day from the Marine Corps Air Station were electronically collected from the Air Force Combat Climatology Center archived historical weather database in Asherville, NC onto a Microsoft Excel spreadsheet. These data were used to assign hourly, mean and peak temperatures and %RH to cases and pre-post controls and to calculate other alternative heat index measurements using the individual temperatures and %RH.

Analytical Methods

The case-crossover design with symmetrical bi-directional (SBI) control sampling was applied to evaluate the association between EHI and heat exposure index. This method compares exposure during the period of time of EHI event with pre- and post-control periods when EHI did not occur. Cases of EHI provided their own control periods (2 per case) for estimation of exposure. Confounding by age, race, gender, fitness, or other personal characteristics was not an issue because the cases were matched on themselves. Conditional logistic regression was used to identify the index most strongly predictive of heat illness. Pearson's product-moment correlation coefficients were used to identify highly correlated pairs of variables so that the chance of multicollinearity could be reduced in the regression models.

The conditional logistic regression models using the PHREG procedure in SAS (16) were applied to the cohort of cases and matched reference periods from the Marine Corps recruit database to estimate cumulative incidence over previous 1 and 2 days of exposure. Male recruits were also stratified by EHI severity to determine if environmental risk factors differed by EHI severity. The selection of cut points for T_{re} were based on our distribution of body core temperatures where $T_{re} \geq 103.1°F$ (39.5°C) was defined as severe EHI severity and $T_{re} < 103.1°F$ (39.5°C) as mild EHI severity. These cut-points of T_{re} are justified by study evidence alone and the distribution of these cut-points is presented in the results section of Chapter 3.

The use of paired pre- and post-control times in a case-crossover design is a relatively new idea (12), so we checked the validity of this approach by comparing single risk models including only pre- or post-control data.

RESULTS

Characteristics of EHI Cases and Hot Temperature Conditions at Parris Island

The demographic characteristics of the recruits are provided in Table 2.1. There were 2069 cases of exertional heat illness (EHI) of which 11% were women and 89% men. The majority of the recruits were white (73%) with 24.5% African-American and 2.5 other (Hispanic, Asian, etc).

Table 2.1. Descriptive statistics on cases of EHI used in case-crossover analyses.

Total Number	2069
Gender, %	
Male	10.8
Female	89.2
Race, %	
White	73.0
African-American	24.5
Other	2.5

The hourly WBGT (that is, the WBGT at the hour immediately preceding a heat illness) on control days was on average about 2°F cooler than on case days (76.61°F and 77.32°F for pre and post-control days vs 79.38°F for case days, Table 2.2). A similar difference of 1 to 2°F on average was observed for previous day mean and peak WBGT, and 2nd day previous mean (2 days before the event day) and peak WBGT (Table 2.2). The same approximate relations held as well for air and radiant temperatures: wet bulb temperature (T_{nwb}), black globe temperature (T_{bg}), and dry bulb temperature (T_a). Data were also available for percent relative humidity (%RH), not a component of WBGT, but a potentially pertinent factor, which was investigated in alternative indices. In this instance, the difference in %RH was somewhat similar between case and control days and variation in %RH did not follow the same pattern as WBGT and it's components (Table 2.2).

Table 2.2. Mean WBGT and Component temperatures for case and control days.

WBGT Temp (°F)	Case Day (n=2069)	Pre-Control Day (n=1970)	Post-Control Day (n=1942)
Hourly WBGT	79.38 ± 7.17	76.61 ± 8.92	77.32 ± 8.39
Mean WBGT_1[1]	81.66 ± 6.96	79.55 ± 8.36	80.38 ± 7.77
Mean WBGT_2[2]	81.19 ± 7.46	79.47 ± 8.28	80.49 ± 7.46
WBGT Temp (°F)	Case Day (n=2069)	Pre-Control Day (n=1970)	Post-Control Day (n=1942)
Peak WBGT_1[3]	85.48 ± 6.89	83.40 ± 8.25	84.22 ± 7.69
Peak WBGT_2[4]	85.76 ± 7.34	83.31 ± 8.10	84.33 ± 7.34

Days with an Available Black Globe Temperature

WBGT (°F) & Components	Case Day (n=1872)	Pre-Control Day (n=1679)	Post-Control Day (n=1655)
Hourly WBGT	79.49 ± 6.98	76.57 ± 8.81	77.32 ± 8.34
T_a	80.33 ± 7.66	77.41 ± 9.10	78.05 ± 8.53
T_{nwb}	72.78 ± 6.11	69.90 ± 8.30	70.88 ± 7.62
T_{bg}	102.54 ± 14.07	99.51 ± 14.43	99.48 ± 14.97
%RH	70.56 ± 15.32	69.34 ± 15.26	70.91 ± 15.30

[1] Previous Day Average WBGT from 7 am to 4 pm.
[2] Previous 2nd Day Average WBGT from 7 am to 4 pm.
[3] Previous Day Peak WBGT.
[4] Previous 2nd Day Peak WBGT.

Male cases experienced somewhat higher mean WBGT temperatures than female cases (Table 2.3).

Table 2.3. Means of EHI hourly case WBGT and mean/peak previous day WBGT temperatures by gender.

Heat Index (°F)	Male Cases (n=1840)	Female Cases (n=222)
WBGT[1]	79.46 ± 6.91	78.79 ± 9.03
Mean WBGT_1[2]	81.72 ± 6.88	81.21 ± 7.54
Mean WBGT_2[3]	81.24 ± 7.47	80.81 ± 7.40
Peak WBGT_1[4]	85.54 ± 6.83	85.00 ± 7.41
Peak WBGT_2[5]	85.12 ± 7.34	84.64 ± 7.30

[1] Hourly Case WBGT.
[2] Previous Day Average WBGT from 7 am to 4 pm.
[3] Previous 2nd Day Average WBGT from 7 am to 4 pm.
[4] Previous Day Peak WBGT.
[5] Previous 2nd Day Peak WBGT.

Also, white male cases experienced slightly higher mean WBGT temperatures than African-American male cases (Table 2.4). Female recruits were not stratified by race because the number of female cases was very small (n = 222).

Table 2.4. Means of EHI hourly case WBGT and mean/peak previous day WBGT temperatures by male recruit race*.

Heat Index (°F)	White Cases (n=1348)	African-American* Cases (n=446)
Hourly WBGT[1]	79.67 ± 6.89	78.81 ± 6.69
Mean WBGT_1[2]	81.78 ± 6.98	81.52 ± 6.42
Mean WBGT_2[3]	81.29 ± 7.54	81.09 ± 7.07
Peak WBGT_1[4]	85.61 ± 6.94	85.35 ± 6.36
Peak WBGT_2[5]	85.15 ± 7.43	84.99 ± 6.88

[1] Hourly Case WBGT.
[2] Previous Day Average WBGT from 7 am to 4 pm.
[3] Previous 2nd Day Average WBGT from 7 am to 4 pm.
[4] Previous Day Peak WBGT.
[5] Previous 2nd Day Peak WBGT.
*Race = Other races excluded.

The temperature components that make up the hourly WBGT were generally highly correlated with one another ($r \geq 0.83$), except for T_{nwb} and T_{bg}, which were less correlated ($r = 0.61$) (Table 2.5).

Table 2.5. Correlation coefficients of hourly components of WBGT (all case and control day measurements).

WBGT Indicators	T_a	T_{nwb}	T_{bg}
T_a, °F	-	.85	.83
T_{nwb}, °F	.85	-	.61
T_{bg}, °F	.83	.61	-
%RH	-.29	.24	-.44

Percent relative humidity was not as well correlated with the WBGT components. Correlations among hourly WBGT and mean/peak previous and 2nd day previous WBGT were all moderately high ($r \geq 0.67$), as expected (Table 2.6).

Table 2.6 Correlations of hourly WBGT and mean and peak WBGTs on previous day.

WBGT Temp* (°F)	Hourly WBGT	Mean WBGT1	Mean WBGT2	Peak WBGT1
Hourly WBGT	-	.70	.67	-
Mean WBGT1[1]	.70	-	.88	-
Mean WBGT2[2]	.67	.88	-	-
Peak WBGT1[3]	.69	.98	.86	-
Peak WBGT2[4]	.65	.87	.98	.86

[1] Previous Day Average WBGT from 7 am to 4 pm.
[2] Previous 2nd Day Average WBGT from 7 am to 4 pm.
[3] Previous Day Peak WBGT.
[4] Previous 2nd Day Peak WBGT.

Prediction of Marine Recruit EHI Risk by Heat Index and Components

We first estimated EHI risk during the 12 weeks of basic training from a continuous conditional logistic regression model containing only WBGT (Table 2.7).

Table 2.7. EHI risk and cumulative heat effects, estimated from case-crossover analyses using both pre- and post-event control days.

Model	Risk Factor	-2 Log L	P value***	All Recruits Odds Ratio[1] (95% CI)
1	WBGT*	4057.07	-	1.11 (1.10 – 1.13)
2	WBGT Mean WBGT_1	4036.51	< .001	1.10 (1.08 – 1.11) 1.03 (1.02 – 1.05)
3	WBGT WBGT*MWBGT_1	4024.71	< .001	1.05 (1.02 – 1.07) 1.01 (1.00 – 1.01)
4	WBGT Mean WBGT_2	4051.91	< .02	1.11 (1.09 – 1.12) 1.02 (1.00 – 1.03)
5	WBGT WBGT*MWBGT_2	4048.52	< .02	1.08 (1.06 – 1.11) 1.00 (1.00 – 1.00)
6	WBGT Mean WBGT_1 Mean WBGT_2	4035.66	< .001	1.10 (1.08 – 1.11) 1.04 (1.02 – 1.06) 0.99 (0.98 – 1.01)
7	WBGT MWBGT_1*MWBGT_2	4040.20	< .001	1.10 (1.08 – 1.11) 1.00 (1.00 – 1.00)
8	WBGT Peak WBGT_1	4039.60	< .001	1.10 (1.08 – 1.11) 1.03 (1.02 – 1.04)
9	WBGT WBGT*PWBGT_1	4030.11	< .001	1.05 (1.03 – 1.08) 1.00 (1.00 – 1.01)
10	WBGT Peak WBGT_2	4050.84	< .01	1.10 (1.09 – 1.12) 1.02 (1.00 – 1.03)
11	WBGT Peak WBGT_1 Peak WBGT_2	4039.60	< .001	1.10 (1.08 – 1.11) 1.03 (1.01 – 1.05) 1.00 (0.98 – 1.02)
12	WBGT PWBGT_1*PWBGT_2	4040.80	< .001	1.10 (1.08 – 1.11) 1.00 (1.00 – 1.00)
13	WBGT WBGT*SEX[2]	3393.43		1.13 (1.11 – 1.15) 0.92 (0.93 – 1.02)
14	WBGT WBGT*RACE[3]	3003.32		1.15 (1.12 – 1.17) 0.95 (0.92 – 0.98)

[1] Cases/Controls All Recruits: 2062/ 3912.
[2] SEX: male=0 and female=1.
[3] RACE: white=0 and African-Americans=1;
*Measured just prior to event.
**WBGT_1 and WBGT_2 refer to measures on the previous day and day before person day, respectively.
***p-value for chi-square test for improvement in –2LL statistic, compared to model 1.

This initial model included all study recruits (2062 cases and 3912 pre and post controls). The number of controls, in most analyses, was not twice that of cases since WBGT and components were not available for every day of each year. Hourly WBGT was a strong predictor of EHI risk ($p < 0.0001$) for all Marine recruits at MRDC-PI during the 12 weeks of basic training. The model predicted an 11% increase in risk per degree Fahrenheit. The validity of this approach was confirmed by comparing single risk models including only pre- or post-control data. Both models predicted risk of EHI quite similarly with odds ratios and confidence intervals in good agreement (Table 2.8).

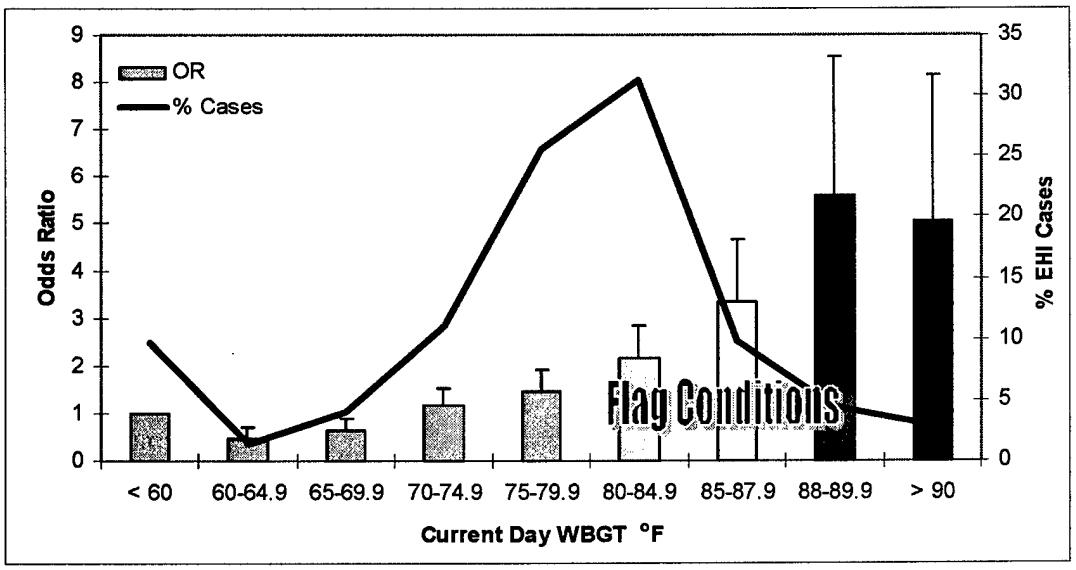
Table 2.8. EHI risk and hourly WBGT. Models comparing pre- and post-event control days.

Risk Factor	-2 Log L	Odds Ratio[1] (95% CI)
WBGT (°F) with Pre-event control days	2242.75	1.15 (1.13 – 1.17)
WBGT (°F) with Post-event control days	2412.10	1.10 (1.08 – 1.11)

[1] Cases with Pre- and Post-Controls: 1850/1850.

Next, a categorical model was fit comparing risk among 8 categories of WBGT (the 4 established flag condition ranges for green, yellow, red and black and the 4 lower 5° intervals). The reference category was WBGT < 60°F. Hourly WBGT was again strongly associated ($p < 0.005$) with risk of EHI rising rather smoothly from the lowest WBGT category (Figure 2.1). We found that risk of EHI more than doubled (OR = 2.17) at the presumed safe green flag level of 80 to 84.9°F.

Figure 2.1. Risk of EHI by temperature conditions.



The percentages of all EHI cases occurring in each WBGT category are shown in Figure 2.1. One can see that 52% of EHI cases occurred below the assumed safe flag conditions, and an additional 31% of EHI cases during green flag conditions. Thus a total of 83% of EHI cases occurred during presumably safe training conditions.

The possibility of a cumulative effect of WBGT on EHI risk was investigated by adding additional WBGT parameters for the previous day and 2nd day previous to the above continuous conditional logistic regression model (Table 2.7). By including previous day mean in the model (model 2), the fit was significantly improved, (the improvement in the –2 log likelihood statistic comparing models 2 and 1 had a p-value of < 0.001). An alternative model substituted an interaction term (WBGT*Previous Day Mean WBGT) in place of previous day mean WBGT, which further improved model fit (model 3, Table 2.7). The interaction term was positive, suggesting that at high hourly WBGT and previous day mean WBGT, the effects of these two variables on risk are no longer independent; but that their combined effect is somewhat higher than would be predicted on the basis of the main effect of WBGT and previous day mean WBGT alone. This finding suggests that there was a cumulative effect of previous day and current day heat exposure in these Marine recruits. When previous 2nd day mean WBGT alone was entered into the model with hourly WBGT, the model fit was improved (model 4, Table 2.7), although not as strongly as when previous day mean was used. An interaction term between hourly WBGT and previous 2nd day mean did not improve model fit (model 5). Adding previous 2nd day mean WBGT to model 2 did not improve model fit (model 6). Substituting the interaction term (Previous Day Mean WBGT* Previous 2nd day Mean WBGT) into model 6 in place of previous day and previous 2nd day mean WBGT did not improve model fit (model 7, Table 2.7).

The same analyses were run using previous day and previous 2nd day *peak* WBGT with similar results (models 8 through 12, Table 2.7). Improvements in model fit when peak WBGT on previous days were added to the WBGT model were not as strong as when means were used.

Interaction terms (WBGT*SEX and WBGT*RACE) were entered in the above WBGT model (model 1, Table 2.8) one at a time to determine if gender and/or race modified the effect of WBGT. There were fewer data available for models including these demographic factors, as noted above, and so the goodness of fit statistics for models including gender or race cannot be directly compared to model 1 in Table 2.8. The simple WBGT model, corresponding to model 1, but including only the subset of data for which gender and race were available had a –2 log likelihood statistic of 3394.82. Model 13 shows that gender is not an effect modifier, as the WBGT-sex interaction term was not different from zero. However, race was found to be an effect modifier, in that African-American recruits appeared to have a somewhat lower risk of EHI per degree WBGT, when compared to white recruits (Table 2.8, model 14). The risk for whites was 1.15 per degree Fahrenheit of WBGT, while for African-Americans, the risk was $\exp(\ln(1.15) + \ln(0.95)) = 1.09$ per degree Fahrenheit of WBGT.

The components of WBGT (as well as %RH) were then entered into logistic regression models, to determine whether an alternative index might predict EHI risk better than WBGT itself. Two basic sets of predictors were investigated: the WBGT components T_{nwb}, T_{bg} and T_a; and the alternative set which substituted %RH for T_{nwb}. Percent relative humidity was substituted for T_{nwb} to determine if an alternative heat index with an easily accessible measure of water vapor was just as good as predicting risk of EHI as an index with T_{nwb}. This dataset was smaller than the full set used for Table 2.7 models since the component temperatures were not available for all hours of each day, reducing the number of available cases (1872) and controls (3334) for analysis. When the 3 WBGT components were used as independent predictors of EHI, a better fitting model resulted, when compared to the model using WBGT itself (Table 2.9 -- compare models 1 and 5). Both T_{nwb} and T_a were strongly associated with risk of EHI, while T_{bg} was only moderately associated with EHI. Excluding T_{bg} (model 2), resulted in an overall fit that was nearly as good. Eliminating T_{bg} gave a simpler expression for predicting risk of EHI that was nearly as good as the model using all 3 components, and also better fitting than the model using WBGT itself.

An alternative components model substituted %RH for T_{nwb} (model 3, Table 2.9). Both %RH and T_a were strongly associated with risk of EHI, and there was again only modest contribution to EHI risk from T_{bg}. Excluding T_{bg} from this model caused only a small reduction in goodness of fit (compared models 3 and 4). The simple model using just %RH and T_a to predict EHI risk fit the data substantially better than WBGT.

Table 2.9. EHI risk, WBGT, component temperatures, and alternative heat indices.

Model	Risk Factor	-2 Log L	P value*	All Recruits Odds Ratio[1] (95% CI)
1	T_{nwb} T_{bg} T_a	3475.70	< .01	1.05 (1.03 – 1.08) 1.01 (1.00 – 1.02) 1.06 (1.03 – 1.09)
2	T_{nwb} T_a	3478.15	< .01	1.05 (1.02 – 1.07) 1.08 (1.05 – 1.10)
3	%RH T_{bg} T_a	3473.37	< .002	1.02 (1.01 – 1.02) 1.01 (1.00 – 1.02) 1.11 (1.09 – 1.13)
4	%RH T_a	3475.96	< .002	1.01 (1.01 – 1.02) 1.12 (1.10 – 1.14)

Heat Indices

Model	Risk Factor	-2 Log L	P value*	ALL Recruits Odds Ratio[1] (95% CI)
5	WBGT*	3485.12	-	1.12 (1.10 – 1.14)
6	WBDT[2]	3478.15	-	1.13 (1.11 – 1.14)
7	RHDT[3]	3475.96	-	1.14 (1.12 – 1.16)

[1] Cases/Controls All Recruits: 1872/ 3334.
[2] Wet Bulb Dry Temperature.
[3] Relative Humidity Dry Temperature.
*Measured just prior to event.
**p-value from chi-square test for improvement in –2LL statistic, compared to model 5.

Using the results of these models, we created two new measures of heat stress risk, modeled on the WBGT. The first, called the Wet Bulb Dry Temperature (WBDT), was based on model 2 in Table 2.9. To get appropriate weightings of each component in the new heat indices, beta coefficients from the previous component models were used to calculate the weights. The coefficients of T_{nwb} and T_a ($ß_{nwb}$ and $ß_a$ respectively) from that model were re-expressed as fractions according to the following equation:

$$f_{nwb} = ß_{nwb} / (ß_{nwb} + ß_{a)} \quad \text{and} \quad f_a = ß_a / (ß_{nwb} + ß_a) \tag{2.1}$$

Then, WBDT was calculated as:

$$WBDT = f_{nwb} * T_{nwb} + f_a * T_a \tag{2.2}$$

The weights of the WBDT were: T_{nwb} 39% and T_a 61%, while the weights of the current WBGT were: T_{nwb} 70%, T_{bg} 20% and T_a 10%. A second new measure was created in a similar way, from model 4, called the Relative Humidity Dry Temperature (RHDT), having weights of %RH 11% and T_a 89%. Models predicting EHI risk with these new indices (models 6 and 7, Table 2.9) fit identically to the previous models upon which they were based, which must be true because the indices in models 6 and 7 are simple linear combinations of the predictors in models 2 and 4. The new simpler indices are

about as strongly associated with risk than WBGT, as evidenced by their odds ratios (compare model 5 to models 6 and 7), and they fit the EHI risk data better, as evidenced by the –2LL statistics. The percent improvement in predicting risk of EHI was approximately 2 to 3% when we compared the new heat indices to the current standard (WBGT). This was done by calculating the difference between the two indices and dividing by the standard (WBGT), and then multiplying the whole expression by 100 to get percent improvement.

These models were further stratified by gender to determine if prediction of EHI using these heat indexes differed for male and female recruits (Table 2.10).

Table 2.10. EHI risk and heat exposure by gender.

Model	Risk Factor	-2 Log L	Males Odds Ratio[1] (95% CI)	-2 Log L	Females Odds Ratio[1] (95% CI)
1	T_{nwb}		1.06 (1.03 – 1.09)		1.00 (0.93 – 1.07)
	T_{bg}	3087.23	1.01 (1.00 – 1.03)	384.28	0.98 (0.94 – 1.02)
	T_a		1.05 (1.02 – 1.08)		1.13 (1.04 – 1.23)
2	%RH		1.02 (1.01 – 1.03)		1.02 (0.98 – 1.02)
	T_{bg}	3084.95	1.02 (1.00 – 1.03)	384.26	0.98 (0.94 – 1.02)
	T_a		1.11 (1.08 – 1.13)		1.13 (1.07 – 1.20)

		Heat Indices			
			Males		Females
Model	Risk Factor	-2 Log L	Odds Ratio[1] (95% CI)	-2 Log L	Odds Ratio[1] (95% CI)
3	WBGT	3092.64	1.13 (1.11 – 1.14)	391.29	1.10 (1.06 – 1.14)
4	WBDT	3091.21	1.13 (1.11 – 1.15)	385.26	1.11 (1.07 – 1.15)
5	RHDT	3089.16	1.14 (1.12 – 1.16)	385.19	1.11 (1.07 – 1.15)

[1] Cases/Controls Males: 1666/2963 Females: 206/361.

For females, only T_a appeared to be an important predictor of risk. Despite this, all 3 indices (WBGT, WBDT and RHDT) showed similar strengths of association with EHI risk among males and females, with only slightly weaker associations evident for females. Since female cases were found to be predominately of mild severity, we also compared male and female risk prediction models restricted to only mild EHI cases (Table 2.11).

Table 2.11. Mild EHI risk and heat exposure by gender.

Model	Risk Factor	-2 Log L	Males Odds Ratio[1] (95% CI)	-2 Log L	Females Odds Ratio[1] (95% CI)
1	T_{nwb}		1.02 (0.96 – 1.08)		1.09 (0.92 – 1.30)
	T_{bg}	701.86	1.03 (1.00 – 1.06)	119.33	1.03 (0.96 – 1.10)
	T_a		1.04 (0.97 – 1.12)		0.96 (0.80 – 1.16)
2	%RH		1.00 (0.99 – 1.02)		1.02 (0.98 – 1.07)
	T_{bg}	702.02	1.01 (1.00 – 1.06)	119.46	1.02 (0.95 – 1.10)
	T_a		1.06 (1.01 – 1.11)		1.04 (0.94 – 1.16)

Heat Indices

Model	Risk Factor	-2 Log L	Males Odds Ratio[1] (95% CI)	-2 Log L	Females Odds Ratio[1] (95% CI)
3	WBGT	705.98	1.10 (1.07 – 1.14)	119.55	1.07 (1.01 – 1.15)
4	N_WBGT	701.86	1.09 (1.07 – 1.13)	119.33	1.07 (1.01 – 1.15)
5	N_INDEX	702.02	1.10 (1.07 – 1.13)	119.46	1.09 (1.01 – 1.18)

[1] Cases/Controls Males: 372/734 Females: 58/11.

Again, there was no important difference in prediction of EHI risk for all heat indexes for male and female recruits.

Racial differences in environmental predictors were investigated among male recruits (Table 2.12). Only whites and African-Americans were investigated, as the numbers of other racial/ethnic groups were very small. African-American male EHI risk was not as strongly associated with any of the WBGT components, although the smaller numbers of subjects probably at least partially explains this difference.

Table 2.12. EHI risk and heat exposure by race[2] (males only).

Model	Risk Factor	-2 Log L	White Males Odds Ratio[1] (95% CI)	-2 Log L	African-American Males Odds Ratio[2] (95% CI)
1	T_{nwb}	2215.14	1.08 (1.04 – 1.11)	780.86	1.03 (0.97 – 1.08)
	T_{bg}		1.02 (1.01 – 1.04)		0.99 (0.96 – 1.02)
	T_a		1.04 (1.00 – 1.89)		1.08 (1.21 – 1.15)
2	%RH	2211.72	1.02 (1.01 – 1.03)	780.86	1.01 (0.99 – 1.02)
	T_{bg}		1.02 (1.01 – 1.04)		0.99 (0.96 – 1.02)
	T_a		1.11 (1.08 – 1.14)		1.10 (1.06 – 1.15)

Heat Indices

Model	Risk Factor	-2 Log L	White Males Odds Ratio[1] (95% CI)	-2 Log L	African-American Males Odds Ratio[2] (95% CI)
3	WBGT	2217.13	1.15 (1.12 – 1.17)	786.19	1.09 (1.06 – 1.12)
4	WBDT	2222.14	1.15 (1.12 – 1.17)	781.27	1.10 (1.07 – 1.13)
5	RHDT	2219.79	1.16 (1.14 – 1.19)	781.26	1.10 (1.07 – 1.13)

[1] Cases/Controls White Males: 1216/2159 [2] African-American Males: 409/732, excluding other races.

There were very few severe female cases (see chapter 3), and so we present analyses stratified by case severity only for males (Table 2.13).

Table 2.13. EHI risk and heat exposure: mild and severe cases.

Model	Risk Factor	-2 Log L	Mild EHI[1] Odds Ratio[3] (95% CI)	-2 Log L	Severe EHI[2] Odds Ratio[3] (95% CI)
1	T_{nwb}	701.86	1.02 (0.96 – 1.08)	593.68	1.05 (0.98 – 1.12)
	T_{bg}		1.03 (1.00 – 1.06)		1.00 (0.97 – 1.04)
	T_a		1.04 (0.97 – 1.12)		1.04 (0.95 – 1.13)
2	%RH	702.02	1.00 (0.99 – 1.02)	593.53	1.01 (1.00 – 1.03)
	T_{bg}		1.01 (1.00 – 1.06)		1.01 (0.97 – 1.04)
	T_a		1.06 (1.01 – 1.11)		1.08 (1.03 – 1.14)

Heat Indices

Model	Risk Factor	-2 Log L	Mild EHI[1] Odds Ratio[3] (95% CI)	-2 Log L	Severe EHI[2] Odds Ratio[3] (95% CI)
3	WBGT	705.98	1.10 (1.07 – 1.14)	594.18	1.09 (1.05 – 1.12)
4	WBDT	705.23	1.10 (1.07 – 1.13)	593.77	1.09 (1.05 – 1.13)
5	RHDT	705.99	1.10 (1.07 – 1.13)	593.62	1.10 (1.06 – 1.14)

[1] Core body temperature (Tre) < 103.1°F.
[2] Core body temperature (Tre) ≥ 103.1°F.
[3] Cases/Controls Mild EHI: 372/738 Severe EHI: 311/616.

Even among males, the available data were quite limited, however, because core body temperature was available for only a small subset (about 33%) of all EHI cases.

The component temperature models are imprecisely estimated for both mild and severe EHI. The 3 indices, however, show remarkably similar association with EHI risk for both mild and severe cases (Table 2.13).

Risk of EHI for Marine Recruits by WBGT Conditions at Parris Island

Risk of EHI was found to be associated not only with current temperatures, but with those of the previous day as well (Table 2.8). To illustrate this cumulative effect, we used model 3 in Table 2.8 to generate odds ratios representing the relative risk of EHI for various combinations of current and previous day WBGT. This table of odds ratios is presented in the final chapter and allows one to investigate the effect of two very hot days in a row, compared to a very hot day followed by a cooler one, or other combinations.

DISCUSSION

Overall, we found current WBGT to be an important predictor for risk of exertional heat illness (EHI) during the 12 weeks of basic training at Marine Corps Recruit Depot, Parris Island (MCRD-PI) for all Marine recruits. Furthermore, the majority (52%) of EHI cases were found to occur below established "safe" flag conditions – a green flag is flown when it is in the range from 80°F to 84.9°F (26.7 to 29.4°C). Kark et al (1996) also reported similar findings in a previous study using a smaller cohort of these same Marine recruits. This high number of EHI cases occurring below established flag conditions, lead us to investigate a possible cumulative effect from the previous day's WBGT.

Including the previous day mean WBGT in our models improved prediction of EHI risk, and substituting an interaction term (Current WBGT*Previous Day Mean WBGT) improved prediction of EHI risk even more. These results suggest that the combined effect of current day and previous day WBGT was more important in predicting risk of EHI than current day WBGT alone. The interaction term suggests the importance of a cumulative effect of previous day and current day WBGT in predicting risk of EHI in these marine recruits. Adding information on heat two days before event (called previous 2nd day) did not further improve risk prediction in this cohort of marine recruits. This suggests that no additional information on risk is gained by going further back than the day before training. A similar increase in prediction of EHI risk was also observed using previous day peak WBGT as well, but the model did not fit quite as well, and so the previous day average was preferred.

Race was found to be an effect modifier in this case-crossover study. White recruits were found to have a 15% increase in EHI risk per degree Fahrenheit of WBGT, while for African-American recruits, there was a 9% increase in EHI risk per degree Fahrenheit of WBGT.

Once we determined that there was a cumulative effect on risk of EHI, our next goal was to determine if we could improve upon the WBGT as a heat index for predicting EHI risk. The WBGT is a weighted average of the natural wet bulb temperature (T_{nwb}), black globe temperature (T_{bg}) and ambient dry temperature (T_a) with weights of: T_{nwb} 70%, T_{bg} 20% and T_a 10%. We used the epidemiologic model of EHI risk to estimate alternative weights for those same temperature components. Alternative weights were found, which predicted risk of EHI somewhat better than the WBGT. One alternative, the WBDT (wet bulb dry temperature) was simpler than WBGT in that it did not include the black globe temperature. Its weights were: T_{nwb} 39% and T_a 61%. A second new index was developed by substituting relative humidity for the wet bulb temperature. This index, the RHDT (relative humidity dry temperature), had weights: %RH 11% and T_a 89%. It fit the EHI data about as well as the WBDT, and better than WBGT. In these new indices, the weighting of heat load is attributed more to the ambient temperature than to either the percent relative humidity or the natural wet bulb. These are relative weightings essentially opposite of those in WBGT, which weights relatively more heavily the wet bulb temperature.

All heat indexes were found to predict risk of EHI similarly for both male and female recruits. However, the relative importance of index components differed somewhat by gender. Only T_a was strongly associated with risk of EHI in female recruits, while both T_{nwb} and T_a were strongly associated with EHI risk and T_{bg} somewhat associated with risk in male recruits. The difference in EHI risk by index components in male and female recruits may have been at least partially explained by gender differences in sweating rates (4), (5).

The possible modifying effects of race could only be investigated in male recruits because of the small number of female recruits in the study. There were no important differences in prediction of EHI for all heat indices, even though index components differed somewhat by race. Only T_a was strongly associated with risk of EHI in African-American male recruits, while all index components were associated with EHI risk in white male recruits. Without additional data, it is difficult to make inferences about this strong effect of ambient temperature (T_a) on African-American male recruits.

Prediction of EHI risk was also examined for male recruits by EHI severity. Model prediction for risk of EHI was the same for both mild and severe EHI for male recruits and index components did not differ by EHI severity. Risk of both mild and severe EHI could be predicted reasonably well using the same heat index. This somewhat surprising result suggests that the severity of a case, as measured by core body temperature, is probably not determined by environmental measures of heat stress, but perhaps instead by characteristics of the individual, or of the physical activity in which she/he was engaged.

Training guidelines based on the WBGT index were developed for military training during the mid 1950's based solely on calisthenics and marching. However, current training involves more intense activities such as running and "war-time" simulations requiring higher activity levels that increase body core temperature, in turn, changing

the ways in which training and environmental conditions interact. It may be that the increased importance of ambient temperature (T_a) in predicting risk (compared to its relatively modest contribution to WBGT) for all recruits result from these changes in training methods. A heat index that accounts for this strong association with T_a would appear to be a better tool for predicting risk of EHI in present day recruit training than the currently used WBGT index.

Advantages of this study were: 1) a large number of EHI events, with nearly complete temperature data, 2) the ability to control for the primary risk factors for EHI: anthropometric measures, physical exertion, training activities, training conditions, and clothing by using a case-crossover design, 3) consistent medical testing and nutritional regimen and no permitted alcohol during training period, which eliminated potential confounding by these variables, and 4) the ability to study both sexes, as well as racial differences.

At the same time the case-crossover design controlled for conditioning and other personal risk factors, it limited our ability to study interactions between environmental factors and conditioning or physical activities at the time of heat illness. The fact that so many of the EHI cases occurred under relatively mild environmental conditions suggests strongly that an effective EHI strategy will have to include more than simply a system of warnings of dangerous heat levels. Table 2.14 and Figure 2.1 show that limiting physical activity during hot periods can substantially reduce EHI risk, but there is clearly no "threshold" below which there is no risk. Identifying such safe conditions for heavy physical activity will require study of the combined effects of heat, physical conditioning, physical activity, clothing, and perhaps other factors as well.

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CHAPTER 3: PARRIS ISLAND STUDY ON SEVERITY PREDICTORS

INTRODUCTION

A number of risk factors have been identified for exertional heat illness (EHI) and heatstroke, related primarily to physical condition, weather and acclimatization 1, (5), (9), (20). Anthropometric and conditioning factors such as body mass index (BMI) and physical fitness test (PFT) run-times have been reported to increase rates of EHI (9). Until now, it has not been examined whether these risk factors operate similarly for mild and severe cases of EHI.

The main objective of this study was to determine if the effects of BMI, PFT run-times, and VO_{2max} on EHI differ by severity level. A secondary objective was to identify specific subgroups of recruits, stratified by BMI and WBGT established flag conditions that were at higher risk of developing EHI at mild heat conditions. A matched case-control study of U.S. Marine recruits was conducted to identify risk factors that predicted both the incidence and the severity of EHI.

METHODS

Study Population

All U.S. Marine recruits who entered basic training at the Marine Corps Recruit Depot Parris Island (MCRD-PI), SC, from 1988 to 1996 were included. Recruits were eligible if they had physical fitness test (PFT) evaluation cards for run-times, sit-ups, and pull-ups for the first week of basic training and were identified by social security number in the personal records of the Marine Corps Automated Recruit Management System (ARMS). The ARMS database is a database that tracks every Marine Corps recruit through basic training. It contains demographic data on gender and race, anthropometric data on height and weight, platoon assignment, date of arrival, platoon change date, and graduation date.

Cases were defined as those recruits in basic training who 1) made an emergency room or clinic visit for exercise-induced heat illness, defined as heatstroke, heat injury, heat exhaustion, heat cramps, exertional dehydration, and/or rhabdomyolysis (15); and 2) had one or more recorded measures of rectal temperature (T_{re}), creatine phosphate kinase (CPK) or systolic (sbp) and diastolic (dbp) blood pressures. Cases were identified through the Navy medical surveillance system at MRCD-PI with use of the NAVMED 6500 form in addition to hospital and clinic records. Cases were excluded if rectal temperature was not recorded at time of episode or during clinic visit (within 20 min of episode).

Controls were all male and female recruits at MCRD-PI without any episodes of EHI during basic training. These platoons are gender-segregated, so that men and woman train independently of one another. Controls were selected from the ARMS database and category-matched to cases by platoon assignment and date of arrival at

Parris Island. Eight controls per platoon were randomly chosen from the ARMS database when possible. When eight or fewer recruits were available from ARMS, then all recruits were used as controls for that specific platoon. To insure that both case and control were in the same platoon at time of an EHI episode, the platoon change date was compared to the date of EHI episodes within that platoon. When it was found that a potential control had changed platoon assignment before an EHI episode had occurred, that recruit was matched to another EHI case in their newly assigned platoon, if present at time of EHI episode. If a recruit's EHI episode took place after a platoon change date, then that recruit became a case in the newly assigned platoon.

Outcome Variables

The outcome measures were diagnosis of exertional heat illness (EHI) defined by incidence of *heatstroke* (ICD-9 code 9920), *heat exhaustion* (ICD-9 code 9924-9925), or *heat cramps* (ICD-9 code 9922) and EHI severity level as indicated by rectal core temperature (T_{re}), mean arterial pressure (MAP) within 5 minutes of EHI episode, and creatine phosphate kinase (CPK) measured within 24 hrs of episode. Field-recorded T_{re} and MAP = $(bp_{dias} + 1/3(bp_{sys} - bp_{dias})$ for cases were identified from the medical corps field incident form for 1988 to 1996. Creatine phosphate kinase was collected for cases at the Parris Island medical clinic for 1988 to 1996. Rectal temperature was considered to be the best measure of heat illness severity because it was recorded either in the field at time of an EHI case episode or at the medical clinic or Beaufort Naval Hospital shortly after EHI episode and remained elevated much longer than blood pressure values. Systolic and diastolic blood pressures were recorded at either the medical clinic or Beaufort Naval Hospital and often 10 to 20 minutes after EHI episode, making MAP a somewhat less reliable measure of severity. Also, CPK values tend to be quite inconsistent from one EHI case to another, which is supported by the large variance presented in the results section of this chapter. Therefore, MAP and CPK were used as secondary measures of EHI severity.

The selection of cut points for T_{re} were based on our distribution of body core temperatures where $T_{re} \geq 103.1°F$ (39.5°C) was defined as severe EHI severity and $T_{re} < 103.1°F$ (39.5°C) as mild EHI severity. These cut-points of T_{re} are justified by study evidence alone and the distribution of these cut-points is presented in the results section of this study.

Cut points for mean arterial blood pressure (MAP) were based on findings from the Framingham Heart Study (6), the Physician's Health Study (23), and an exercise study of conditioned athletes in a hot environment (19). Both Franklin and Sesso reported a resting MAP of approximately 90 mmHg for healthy men and women < 60 years of age. Nybo found a mean MAP of 93 mmHg for 8 endurance cyclists with a mean age of 23 years after 10 min of cycling on an ergometer. Although resting MAP was not available from the Nybo study, all three studies reported a MAP of 90 to 93 mmHg for healthy individuals less than 60 years of age.

In order to define a MAP threshold as a measure of severity of EHI, evidence linking an association between MAP and an adverse health outcome was needed.

Miura et al. (2001) reported an increased risk in overall death rate (RR=1.18, 95% CI 1.10 – 1.27) and cause-specific deaths from CHD (RR=1.23, 95% CI 1.08 – 1.41) and CVD (RR=1.24, 95% CI 1.11 – 1.40) for males < 60 years of age with a mean MAP blood pressure index of 96.8 mmHg compared to blood pressure indexes of pulse pressure, systolic and diastolic blood pressures. Sesso et al. (2000) also found a 2.5 fold increase in risk for cardiovascular disease for men < 60 years of age and a MAP ≥ 97 mmHg compared to men in the same age group with a MAP < 88 mmHg (24). Based on these findings, cut-points for MAP were determined to be ≥ 95 for severe EHI and < 95 MmHg for mild EHI.

Research done at the United States Army Research Institute of Environmental Medicine (USARIEM), Natick, MA, documented CPK levels of ≥ 4000 u/l in Marine recruits with severe symptoms of EHI (C. B. Wenger, personal communication, March 2002). Therefore an arbitrary cut point was selected for CPK ≥ 4000 units/liter (u/l) for severe cases and < 4000 u/l for mild severity cases.

Risk Factors

Available covariates included platoon assignment, gender, age, race, body mass index (BMI) at start of training, indicators of strength and aerobic capacity and categories of WBGT. Gender, race and platoon assignment were considered potential confounders. African-Americans and other races were combined for these analyses because of very small numbers of the other race groups (Asian, Native American, etc.). Age was not found to be a risk factor by Gardner et al. (1996) of recruits aged 17 to 31 years but was included in the analyses.

Strength and aerobic capacity measures consisted of physical fitness tests (PFT) at phase 1 (week 1): a) 0.75-mile run-times (females) and 1.5-mile run-times (males), b) length of time pull-up held within 2 minutes (females), number of pull-ups within 2 minutes (males), c) number of sit-ups within 2 minutes, and d) VO_{2max}. Phase 2 (weeks 5 thru 8) 1.5-mile run-times (females) and 3-mile run-times (males) were used to determine if there was a change in EHI risk from early training (processing week and training weeks 2 thru 4) to late training (training weeks 5 thru 12). Information on PFT scores were collected from recruit training evaluation cards from 1988 to 1996. These evaluation cards are the day-to-day "report card" of each individual recruit for the 12-weeks of basic training.

Analytical Methods

A matched case-control study was applied to examine effects of risk factors on EHI severity. Controls were category-matched to cases by initial platoon assignment. As a consequence, environmental WBGT temperatures were the same for cases and controls, since they underwent training simultaneously for the twelve-week training period. Matching by platoon assignment also controls for differences among drill instructors and seasonal temperatures. Although odds ratios (ORs) stratified by WBGT can be compared, the main effect of environmental heat cannot be estimated. To determine which subgroups of Marine recruits were at higher risk of developing EHI at

mild heat condition, categories of body mass index (BMI) defined by Gardner et al (1996) and WBGT from established military guidelines were stratified to compare ORs (Tables 3.1 and 3.2).

Table 3.1. Categories of body mass index (BMI).

Categories	Male BMI (kg/m^2)*	Female BMI (kg/m^2)
Low	< 22	< 19.8
Medium	22 to < 26	19.8 to < 23.4
High	> 26	> 23.4

*Gardner 1996.

Table 3.2. Categories of the wet bulb glob index (WBGT).

Categories*	WBGT (°F)
Yellow Flag	85 to 87.9
Red Flag	88 to 89.9
Black Flag	≥ 90

*USMC 1980.

Categories for BMI were low BMI < 22 kg/m^2, medium BMI 22 to < 26 kg/m^2 and high BMI > 26 kg/m^2 for male recruits, and where categories for BMI were low BMI < 19.8 kg/m^2, medium BMI 19.8 to < 23.4 kg/m^2 and high BMI > 23.4 kg/m^2 for female recruits. Categories of WBGT were below Green Flag < 80°F (26.7°C), Green Flag 80 to 84.9°F (26.7 to 29.4°C), Yellow Flag 85 to 87.9°F (29.4 to 31.1°C), Red Flag 88 to 89.9°F (31.1 to 32.2°C), and Black Flag > 90°F (32.2°C).

Pearson's product-moment correlation coefficients were calculated among all risk factors, to determine which variables were correlated with one another prior to multivariate regression modeling. Conditional logistic regression was used to model two levels of EHI severity (severe and mild) defined by core body temperature (T_{re}) and/or mean arterial pressure (MAP) at time of EHI episode, and/or creatine phosphate kinase (CPK) level recorded at the medical clinic. If a qualitative similarity between individual

models was found then polytomous logistic regression was applied to the data to estimate odds ratios by severity of exposure.

Binary conditional logistic regression models were used to examine the effects of exertional heat illness (EHI) severity, and to compare odds ratios (ORs) stratified by BMI and WBGT. To determine if there were changes in EHI risk from early to late training, dummy variables were used representing early and late training periods. The conditional logistic regression model using the PHREG procedure in SAS was applied with the goal of finding the best fitting model with the fewest parameters by comparing a reduced model to the appropriate full model containing only those variables found to contribute to risk of EHI (Figure 3.1).

Figure 3.1. Conditional logistic regression.

Full Model*:

$$logit\ P(EHI) = \beta_1(BMI) + \beta_2(RUN_1) + \beta_3(PU_1) + \beta_4(SU_1) + \beta_5(AGE) + \beta_6(RACE)$$

Reduced Model*:

$$logit\ P(EHI) = \beta_1(BMI) + \beta_2(RUN_1) + \beta_3(BMI^* RUN_1)$$

*BMI = body mass index.
RUN_1 = initial run.
PU_1 = initial pull-ups.
EHI = exertional heat illness.
SU_1 = initial sit-ups.
AGE = age at entry into basic training.
RACE = White, African-American, Hispanic, etc.

Models were applied to the overall heat illness cohort and for two levels of EHI severity. Mild and severe levels of EHI severity defined by cut points of T_{re}, CPK and MAP described above.

The most frequently used matched design is one in which each case is matched to a single control, where you have two subjects in each stratum. The conditional likelihood in a one to one matched study is expressed as (10):

$$L_k(\beta) = e^{\beta' x_{1k}} / \ e^{\beta' x_{1k}} + e^{\beta' x_{0k}} \qquad (3.1)$$

where $\mathbf{x_{1k}}$ is the data vector for the case and $\mathbf{x_{0k}}$ is the data vector for the control in the kth stratum of the pair. Here the likelihood models the probability of the covariate values whereas in unconditional logistic regression the likelihood models the probability of the outcome. For our study, a one to M matched study was used with M having 2 or more controls per case changing the above equation to:

$$l_k(\beta) = e^{\beta' x_{k1}} / \ e^{\beta' x_{k1}} + e^{\beta' x_{k2}} + e^{\beta' x_{kn}} \qquad (3.2)$$

where $\mathbf{x_{k1}}$ is the case relative to the number of controls with data $\mathbf{x_{k1}}$, $\mathbf{x_{k2}}$, $\mathbf{x_{kn}}$. It is important that the individual covariate has at least one control with a different value than the case or that stratum will not supply information to estimate that coefficient.

Gardner (1996) reported that race (white vs non-white) was found to have a weak association with EHI (OR = 1.7). Therefore, race was examined as a possible confounder by comparing estimated coefficients for risk factors from models including and not including race. To determine if race was an effect modifier, the full model with interaction terms was compared to a model without interaction terms using the likelihood ratio test (12). If the change in deviance (G statistic) of the full model with interaction terms was statistically significant ($p < 0.05$) then race was considered an effect modifier.

Cardiovascular fitness expressed as a recruit's maximal oxygen uptake (VO_{2max}) was estimated using recruit run-times and gender specific tables of run-times and VO_{2max} from the American Conference of Sports Medicine Guidelines (16). This was done to compare women on the same scale as the men. Since the women's initial PFT 1 run was .75 miles, while the men's was 1.5 miles, a conversion factor of .45 was used to convert the women's run-times from .75 to 1.5 miles (11). Separate linear regressions were used to estimate individual VO_{2max} for both men and women using the information from the ACSM tables. The prediction equation for men was VO_{2max} = 78.32 – (2.90*PFT 1 run) and the prediction equation for women was VO_{2max} = 76.97 – (2.80*(PFT 1 run/0.45)).

Separate categorical conditional logistic regressions were used to estimate odds ratios for categories of BMI and VO_{2max} for male recruits and VO_{2max} for female recruits. BMI was divided into categories of low, medium and high, and VO_{2max} separated into categories of low, medium-low, medium and high. The BMI categories for males were the same as those used in a previous study done on this same population of male recruits by Garner et al (10), where at least 20% of the cases occurred in the high BMI group. Categories for BMI were low BMI < 22 kg/m^2, medium BMI 22 to < 26 kg/m^2 and high BMI > 26 kg/m^2. The categories for low to high VO_{2max} were taken from the guidelines of the American Conference of Sports Medicine (16). For males the categories were low $VO_{2max} \leq 40.98$ ml/min·kg, medium low VO_{2max} 40.98 to < 44.23 ml/min·kg, medium VO_{2max} 44.23 to < 48.20 ml/min·kg and $\geq$ 48.20 ml/min·kg and where categories for VO_{2max} were low $VO_{2max} \leq 33.76$ ml/min·kg, medium low VO_{2max} 33.76 to < 36.65 ml/min·kg, medium VO_{2max} 36.65 to < 40.98 ml/min·kg and $\geq$ 40.98 ml/min·kg for female recruits. These models were then used to calculate odds ratios for each of the combined risk categories.

Absolute risk estimates were expressed as a recruit's risk of developing EHI over the 12 weeks of recruit basic training. Absolute risk is a function of the excess relative risk and the background or baseline risk that occurs in the recruit training population. Excess relative risk (OR–1) was calculated for each risk category from the above odds ratios from the conditional categorical model. The baseline (defined as the risk of EHI in the lowest exposure category—for example low BMI and high VO_{2max}) risk is a function of overall cumulative incidence of EHI that occurs in this population of Marine recruits and the fraction of cases, which occur in the lowest exposure category. Overall EHI cumulative incidence (EHI risk) was calculated from the number of recruit cases and

recruit accessions (entry into basic training), which occurred at the Parris Island Marine Recruit Depot from 1982 to 1991 (13). With an approximation of the background risk, the absolute risks for each risk category could be calculated where:

*Absolute Risk = (Excess Relative Risk*Background Risk) + Background Risk, or*
*Absolute Risk = Relative Risk*Background Risk*

RESULTS

Characteristics of Marine Recruits at Parris Island

The demographic, physical, performance and physiological characteristics of the recruits are provided in Table 3.3.

Table 3.3. Characteristics of Marine recruits.

	Male Cases/Controls	Male Case Means	Male Control Means
AGE, yrs	798/2111	19.85 ± 2.00	19.71 ± 1.92
HEIGHT, m^2	798/2111	1.76 ± 0.07	1.77 ± 0.07
WEIGHT, kg	799/2111	76.96 ± 12.01	73.26 ± 10.88
BMI, kg/m^2	798/2111	24.87 ± 3.23	23.49 ± 3.04
Run[1], min	622/1837	11.84 ± 1.25	11.11 ± 1.17
VO_{2max}[2]	622/1837	43.98 ± 3.64	46.11 ± 3.38
Pull-ups[3]	617/1830	8.59 ± 4.36	9.91 ± 4.37
Sit-ups	622/1839	53.64 ± 11.82	56.04 ± 11.76
Core Body T_{re}, °F	799/-	103.01 ± 2.40	-
MAP, mmHg	777/-	96.20 ± 11.79	-
CPK, u/l	544/-	1670.69 ± 4761	-
% White Race*	798/2111	71.2	80.3

	Female Cases/Controls	Female Case Means	Female Control Means
AGE, yrs	82/222	19.91 ± 2.00	19.86 ± 1.96
HEIGHT, m^2	82/223	1.63 ± 0.07	1.64 ± 0.06
WEIGHT, kg	82/223	57.12 ± 6.50	57.99 ± 6.16
BMI, kg/m^2	82/223	21.53 ± 1.87	21.52 ± 1.86
Run[1], min	48/161	6.53 ± 0.79	6.10 ± 0.83
VO_{2max}[2]	48/161	36.94 ± 4.90	39.01 ± 5.16
Pull-ups[3]	48/161	42.96 ± 17.10	49.07 ± 17.61
Sit-ups	48/161	35.56 ± 8.33	35.91 ± 8.33
Core Body T_{re}, °F	82/-	101.62 ± 2.03	-
MAP, mmHg	79/-	91.30 ± 10.66	-
CPK, u/l	46/-	921.33 ± 2030	-
% White Race*	82/223	62.2	71.9

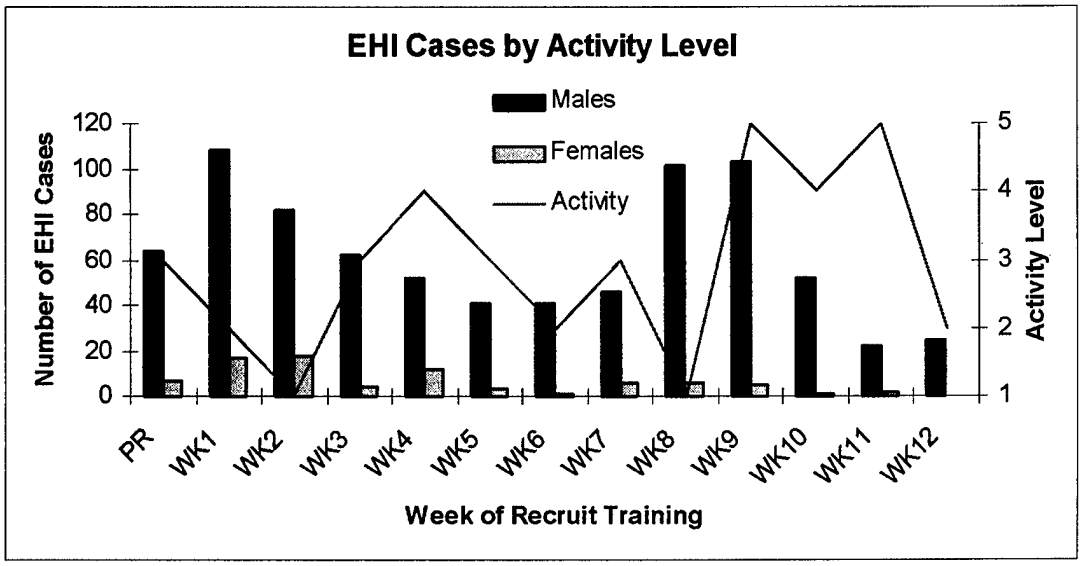
[1] 1.5 mi PFT run for males, 0.75 mi PFT1 run for females.
[2] Estimated from ACSM Guideline Tables 1995, units of measure: ml/min·kg.
[3] Number of repetitions for males, Time in seconds for females.
*All races.

Controls had a faster initial physical fitness test (PFT) 1 run-time than cases (11.11 vs 11.84 minutes for males, and 6.10 vs 6.53 minutes for females). This was also the case for estimated VO_{2max} -- controls had a lower mean VO_{2max} than cases (46.11 vs 43.98 ml/min·kg for males, and 39.01 vs 36.94 for females), where VO_{2max} is defined as maximal oxygen uptake per unit body mass (ml/min·kg). Controls did better in strength training than cases; for example, male controls performed 10 pull-ups and 56 sit-ups vs 9 pull-ups and 54 sit-ups for cases. Female controls where able to hold there pull-up extensions longer than cases -- 49.07 vs 42.96 seconds, but performed a similar number of sit-ups.

Males and females on average were 20 yrs of age. Male cases had higher weights and a greater BMI than controls -- 76.96 vs 73.26 kg, and 24.87 vs 23.49 kg/m^2 respectively, while female controls were only a little heavier than cases -- 58 vs 57.12 kg, and had similar mean BMI than controls -- 21.53 vs 21.52 kg/m^2. Male cases on average had a higher mean core body temperature (T_{re}) than female cases -- 103.01 vs 101.62°F (39.45 vs 38.68°C). White recruits comprised the majority of the cohort – cases (71.2% male, 62.2% female) and controls (80.3% male, 71.9% female).

For male recruits, the numbers of EHI cases were found to be similar for early training (processing week and training weeks 1 thru 4) and late training (training weeks 5 thru 12) (Figure 3.2).

Figure 3.2. Numbers of EHI cases across training weeks 1988 thru 1996 and activity level* by gender.



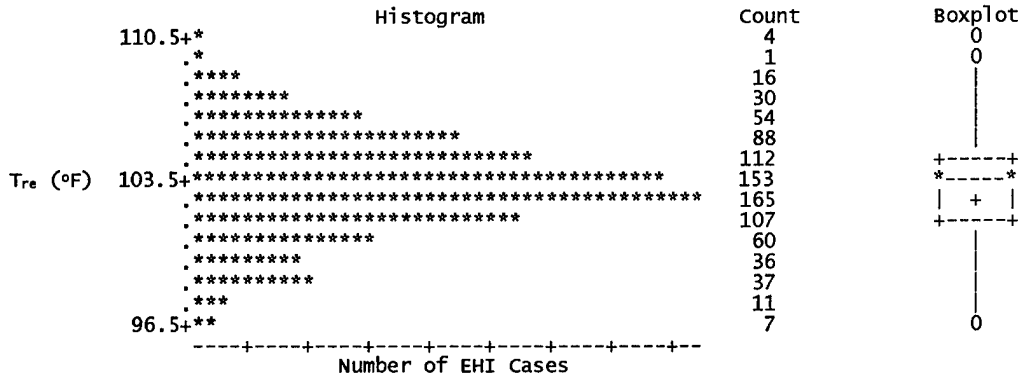
**Processing Week* = haircuts, platoon assignments, physicals, uniforms and ends with the initial PFT.
Week 1 (1st week of training) = combat drills, guard duty, body hardening and a class on customs and courtesies.
Week 2 = first aid training and classes on Marine Corps history.
Week 3 = classes, a day at the obstacle course and end with a 3 mile conditioned march.
Week 4 = self-defense, inspection, and a formation drill.
Week 5 = swimming drills and a 5 mile conditioned march at the end.
Week 6 and 7 = marksmanship training with one day of close order drill and one day on the confidence course.
Week 8 = working in the mess hall or some other similar assignment.
Week 9 = fundamentals of field firing with a 10-mile march with packs.
Week 10 = company drill, Commander's inspections, final PFT and a day of rappelling.
Week 11 = the "Crucible".
Week 12 = inspections, a family run and graduation.

Female recruits were found to have larger numbers of EHI cases in early training than late training. The number of EHI cases does not appear to change by level of weekly training activity (Figure 3.2). The initial week is the in-process week, which consists of haircuts, platoon assignments, physicals, uniforms and ends with the initial physical fitness test (PFT). The formal weeks of training consists of a) Week 1 comprised of close combat drills, guard duty, body hardening and a class on customs and courtesies, b) week 2 consists of first aid training and classes on Marine Corps history, c) the 3rd week is made up of training including more classroom training, a day at the obstacle course and ends with a 3-mile conditioned march, d) week 4 is comprised of training on self-defense, inspection, and a formation drill, e) swimming drills take up most of the 5th week with a 5-mile conditioned march at the end, f) weeks 6 and 7 consists of

marksmanship training with a day of close order drill and another day on the confidence course, g) week 8 is spent working in the mess hall or some other similar assignment, h) the 9th week consists almost entirely of the fundamentals of field firing with a 10-mile march carrying packs, i) week 10 is made up of company drill, Commander's inspections, final PFT and a day of rappelling, j) the "Crucible" (a rigorous 54-hour field training exercise consisting of forced marches, military exercises and sleep deprivation; requiring teamwork, problem solving and physical endurance) takes up most of week 11, k) the last week of training (week 12) consists of inspections, a family run and graduation.

The distributions of body core temperature (T_{re}), mean arterial blood pressure (MAP) and creatine phosphate kinase (CPK) are shown in figures 3.3 to 3.5.

Figure 3.3 Distribution of EHI case rectal temperature (T_{re}) for all EHI cases.



Cut-points for T_{re} were based on this distribution of body core temperatures where $T_{re} \geq$ 103.1°F(39.5°C) was defined as severe EHI and T_{re} < 103.1°F (39.5°C) as mild EHI. Cut-point for MAP was chosen as $\geq$ 95 mmHg for severe EHI and < 95 mmHg for mild EHI based on our results and findings by Miura and Sesso (17), (23). It was not possible to separate CPK into severe and mild EHI severity because only a small number of EHI cases (Fig. 3.5) were found to occur at CPK $\geq$ 4,000 u/l, previously observed in Marine recruits with severe symptoms of EHI (C. B. Wenger, personal communication, March 2002).

Figure 3.4. Distribution of EHI case mean arterial pressure (MAP) for all EHI cases.

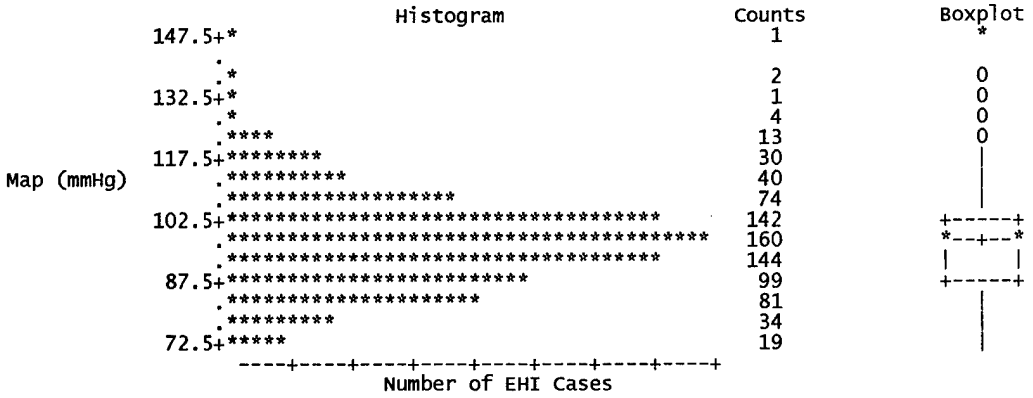
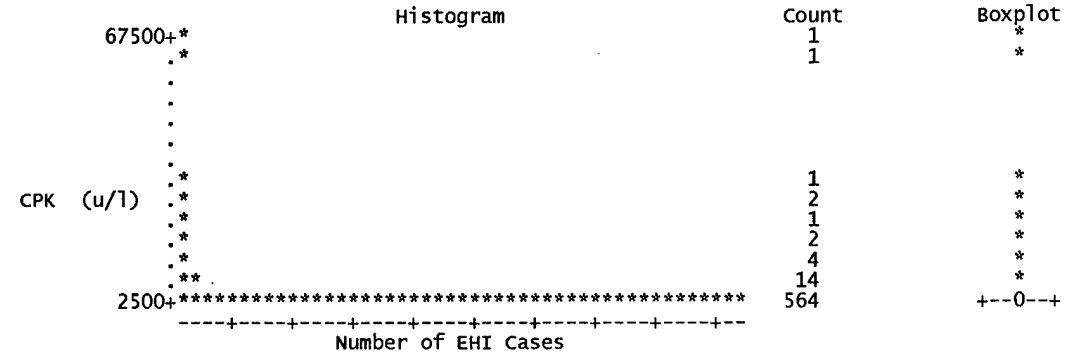


Figure 3.5. Distribution of EHI case creatine phosphate kinase (CPK) for all EHI cases.



Also, since correlations between T_{re} and MAP, and T_{re} and CPK were found to be poor with one another (Table 3.4), we decided not to investigate MAP and CPK as severity factors for EHI.

Table 3.4. Correlations of EHI case severity indicators by gender.

EHI Severity Indicators	Males*			Females*		
	T_{re}	MAP	CPK	T_{re}	MAP	CPK
T_{re}	-	-.01	-.03	-	.21	.03
MAP	-.01	-	.01	.21	-	-.02
CPK	-.03	.01	-	.03	-.02	-

*Male Cases T_{re}: 799 MAP: 777 CPK: 544 Female Cases T_{re}: 82 MAP: 79 CPK: 46.

Measures of EHI Risk of Marine Recruits at Parris Island

Table 3.5 provides the odds ratios and 95% confidence intervals, estimated from a continuous conditional logistic regression model, for developing EHI during the 12 weeks of basic training.

Table 3.5. Initial models for EHI risk among males and females.

Risk Factor	Males Odds Ratio* (95% CI)	Females Odds Ratio* (95% CI)
AGE	1.01 (0.95 – 1.07)	0.90 (0.74 – 1.11)
RACE[1]	1.60 (1.25 – 2.05)	1.96 (0.93 – 4.13)
BMI	1.07 (1.03 – 1.11)	0.90 (0.71 – 1.10)
Run	1.65 (1.48 – 1.85)	2.46 (1.18 – 5.13)
Pull-ups	0.96 (0.96 – 1.02)	0.98 (0.95 – 1.01)
Sit-ups	1.01 (0.99 – 1.07)	1.03 (0.98 – 1.08)

*Cases/Controls Males: 598/1546 Females: 45/110.
[1] Race: white = 0, other = (African-American and other races) = 1.

Results are reported separately by gender. When a single model for males and females was tested, using a gender coefficient, the model did not converge because of the small size of the female cohort. Therefore, conditional logistic models had to be stratified by gender. In these initial models, there were 598 male and 45 female cases matched to 1546 male and 110 female controls. These odds ratios represent the effect on risk for EHI considering its association with other risk factors in the model.

In males, (Table 3.5) BMI, initial PFT run, and race were strongly associated ($p < 0.001$) with risk of EHI, while age, initial PFT pull-ups and sit-ups, and interaction terms were not. Among women, only the initial run-time was strongly associated with risk. Simpler models were then constructed, removing all terms, one at a time. Only BMI and initial PFT run-time and race were found to be important predictors (Table 3.6).

Table 3.6. Initial models for EHI risk among males and females.

Model	Risk Factor	Males Odds Ratio* (95% CI)	Females Odds Ratio* (95% CI)
	RACE[1]	1.57 (1.24 – 2.00)	1.68 (0.82 – 3.46)
1	BMI	1.08 (1.04 – 1.11)	0.95 (0.78 – 1.15)
	Run	1.64 (1.48 – 1.85)	2.48 (1.37 – 4.48)
2	RACE[1]	1.59 (1.25 – 2.03)	1.70 (0.82 – 3.49)
	Run	1.78 (1.61 – 1.96)	2.39 (1.35 – 4.23)
	RACE[1]	0.69 (0.05 – 9.35)	0.02 (0.00 – 430.0)
3	BMI	1.08 (1.03 – 1.12)	0.93 (0.78 – 1.22)
	Run	1.61 (1.48 – 1.81)	2.07 (1.37 – 4.00)
	RACE*BMI	1.00 (0.92 – 1.08)	1.05 (1.37 – 1.61)
	RACE*Run	1.08 (0.87 – 1.35)	1.72 (1.37 – 4.15)

*Cases/Controls Males: 612/1562 Females: 48/131.
[1] Race: white = 0, other = (African-American and other races) = 1.

Among both males and females, initial PFT run-time remained the strongest predictor of risk. In males, BMI and race were also important predictors, but not in females. Race was found not to be a confounder by comparing Table 3.6 to 3.7 (model 1).

Table 3.7. Reduced models for EHI risk among males and females.

Model	Risk Factor	-2 Log L	Males Odds Ratio* 95% CI	-2 Log L	Females Odds Ratio* 95% CI
1	BMI	1570.12	1.07 (1.04 – 1.11)	120.90	0.91 (0.76 – 1.09)
	Run		1.66 (1.50 – 1.83)		2.61 (1.49 – 4.57)
2	Run	1590.97	1.79 (1.63 – 1.97)	121.92	2.41 (1.42 – 4.08)
3	BMI		1.16 (0.83 – 1.85)		1.29 (0.27 – 6.69)
	Run	1569.92	1.94 (0.96 – 3.91)	120.72	8.70 (0.03 – 2215.9)
	BMI*Run		0.99 (0.97 – 1.02)		0.95 (0.74 – 1.21)

*Cases/Controls Males: 612/1562 Females: 48/131.

The interaction term (BMI*Run) was not associated with risk of EHI in either male or female models (model 3, Table 3.7) ruling out effect modification by these two risk factors for all EHI severity. Interaction terms between these two covariates did not improve model fit (-2LL model 3 vs 1), and in females, the model interaction fit quite poorly, as can be seen from the very wide confidence interval for the run-time term in model 3, female.

The potentially modifying role of race was investigated, but only among males because of the small number of female cases (Table 3.8).

Table 3.8. Reduced models for EHI risk among males, separately for whites and non-whites.

Model	Risk Factor	-2 Log L	White Males Odds Ratio* (95% CI)	-2 Log L	Other Males[1] Odds Ratio* (95% CI)
1	BMI	1012.74	1.07 (1.03 – 1.12)	148.37	1.10 (1.00 – 1.22)
	Run		1.58 (1.40 – 1.78)		1.55 (1.14 – 2.11)
2	BMI		1.33 (0.89 – 2.00)		1.57 (0.51 – 4.83)
	Run	1011.58	2.51 (1.06 – 5.94)	148.28	3.21 (0.32 – 32.63)
	BMI* Run		0.98 (0.95 – 1.02)		0.97 (0.88 – 1.07)

*Cases/Controls White Males: 432/1047 Non-White Males: 89/115.
[1] Includes African-Americans and other race groups.

In these analyses, African-Americans and other races were combined due to very small numbers of "other races" in this cohort. These models were estimated from 432 cases and 1047 matched controls for white males and 89 cases and 115 matched controls for non-white males. The results for white and non-white males were quite similar (Table 3.8). The model with only the main effects of BMI and run-time were essentially identical in the two race groups, while the models with an interaction term suggested a somewhat stronger effect of run-time on EHI risk in whites than in non-whites. This difference, however, was not considered further because the interaction terms did not substantially improve model fit (-2LL model 2 vs model 1, Table 3.8), and so the simpler mixed effects models were used. For all EHI severity, a final model with BMI and run-time was found to predict risk of EHI best for male recruits (model 1, Table 3.7), while a model with run-time and race or run-time only predicted risk of EHI well in female recruits (model 2, Tables 3.6 and 3.7). Race was found not to be an effect modifier for risk of EHI in male recruits (Table 3.8).

The possibility that there were different products of more and less severe EHI cases was investigated next. Exertional heat illness cases were classified as severe when their reported core body temperature (T_{re}) was $\geq$ 103.1°F and classified as mild severity when their reported core body temperature (T_{re}) was < 103.1°F. Race was not included in these models, since it was not found to be a confounder or effect modifier in the models of all EHI severity. Among males there were 322 mild EHI cases and 1092 matched controls and 290 severe EHI cases and 997 matched controls. Models could not be fit for female cases in the severe group because of the small number of cases (n = 8). For comparison with the results for males, a mild EHI severity model was run for females (41 cases and 120 matched controls). The first prediction model of Table 3.7 fit both the mild and severe data well (Table 3.9).

Table 3.9. Models for EHI risk among males, separately for mild[1] and severe[2] cases.

Model	Risk Factor	-2 Log L	Mild EHI[1] Odds Ratio (95% CI)	-2 Log L	Severe EHI[2] Odds Ratio (95% CI)
1	BMI	899.93	1.08 (1.03 – 1.13)	756.00	1.08 (1.02 – 1.13)
	Run		1.53 (1.34 – 1.73)		1.85 (1.56 – 2.15)
2	BMI	899.40	0.94 (0.62 – 1.42)	752.27	1.77 (1.07 – 2.94)
	Run		1.15 (0.49 – 2.72)		5.35 (1.78 –15.93)
	BMI*Run		1.01 (0.98 – 1.05)		0.96 (0.92 – 1.00)

*Case/Controls Mild EHI: 322/1092 Severe EHI: 290/997.
[1] Core body temperature (Tre) < 103.1°F.
[2] Core body temperature (Tre) ≥ 103.1°F.

However, the second model of Table 3.7 did not improve model fit for mild severity (-2 LL, Table 3.9), while risk of severe EHI was strongly associated with BMI, run-time, and the interaction between the two (Table 3.9). The interaction term was negative, suggesting that at high BMI and long run-times, the effects of these two variables on risk are no longer independent; but that their combined effect is somewhat less than would be predicted on the basis of the main effect of BMI and run-time alone. The lack of increased model fit (model 2, Table 3.9) to the mild EHI cases was not due to small numbers – there were roughly equal numbers of cases in both severity groups. Mild EHI risk was compared for males and females (Table 3.10).

Table 3.10. Reduced models for mild EHI risk among males and females.

Risk Factor	Males* Odds Ratio (95% CI)	Females* Odds Ratio (95% CI)
BMI	1.08 (1.03 – 1.13)	0.91 (0.76 – 1.09)
Run	1.53 (1.34 – 1.73)	2.57 (1.44 – 4.60)

*Cases/Controls Males: 322/1092.
*Cases/Controls Females: 41/120.

As in previous analyses of all EHI cases regardless of severity, there was no evidence of an effect of BMI in women. The effect of run-time appeared somewhat stronger in women than in men, but the wide confidence interval on the effect in women indicates that one should be cautious in interpreting this apparent difference. Since individual models for severity did not show evidence of qualitative similarity, we were not able to apply polytomous conditional logistic regression to the data.

The differences in the risk prediction models for males and females (Table 3.10) might be partially explained by differences in the run-time tests given to male and female recruits. To investigate this further, models were fit using a measure of conditioning, the estimated VO_{2max} instead of the initial run-time (Table 3.11).

Table 3.11. Reduced models for EHI risk among males and females BMI and VO_{2max}.

Risk Factor	Males Odds Ratio* (95% CI)	Females Odds Ratio* (95% CI)
BMI	1.07 (1.04 – 1.11)	0.91 (0.76 – 1.09)
VO_{2max}	0.84 (0.81 – 0.87)	0.86 (0.78 – 0.94)

*Cases/Controls Males: 612/1652 Females: 48/131.

The coefficients estimating the association between VO_{2max} and EHI risk for males and females were essentially the same, suggesting this model provides a better estimate of the effect of conditioning on risk than initial run-time. The BMI continued to show no association with risk among females in this model.

Fitness will generally improve during training, so that the initial BMI and run-time measures may not be accurate predictors of risk of EHI during the later weeks of training. As noted in the methods, there is a 2nd PFT run-time test in training week 5. Body mass index though was only available in the week prior (processing week) to the first week of the 12-week training session. These models were fit only for males.

Episodes of EHI for men in late training peaked during training weeks 9 and 10 with 101 and 103 case consecutively, which represent 58% of EHI cases in late (training weeks 5 thru 12) training and 26% of total EHI cases. Risk of EHI during early (processing week and training weeks 1 thru 4) training was investigated with a model using BMI, initial run-time, and the interaction of these two terms (Table 3.12).

Table 3.12. Models for EHI risk among males, by time of occurrence[1], separately for mild[2] and severe[3] cases.

Model	Time of Occurrence[1]	Risk Factor	Odds Ratios (95% CI) All EHI	Mild EHI[2]	Severe EHI[3]
1	All* Training	BMI	16 (0.83 – 1.61)	94 (0.62 – 1.42)	1.77 (1.07 – 2.94)
		Run	94 (0.96 – 3.91)	15 (0.49 – 2.72)	5.35 (1.78 – 15.9)
		BMI*Run	99 (0.97 – 1.02)	01 (0.98 – 1.05)	0.96 (0.92 – 1.00)
2	Early** Training	BMI	48 (0.93 – 2.37)	19 (0.68 – 2.10)	2.57 (1.21 – 5.46)
		Run	99 (1.07 – 8.33)	92 (0.56 – 6.54)	9.35 (1.77 – 49.4)
		BMI*Run	98 (0.94 – 1.02)	99 (0.95 – 1.04)	0.94 (0.88 – 1.00)
3	Late*** Training	BMI	02 (0.97 – 1.07)	07 (0.99 – 1.14)	0.99 (0.92 – 1.06)
		Run	17 (1.80 – 2.62)	61 (1.28 – 2.02)	3.33 (2.39 – 4.36)
		% Run Improvement	93 (0.90 – 0.96)	96 (0.92 – 1.00)	0.89 (0.85 – 0.93)

*Case/Controls All EHI: 612/1652 Mild EHI: 322/1092 Severe EHI: 290/ 997.
**Case/Controls All EHI: 305/783 Mild EHI: 176/453 Severe EHI: 127/410.
***Case/Controls All EHI: 286/808 Mild EHI: 130/457 Severe EHI: 157/509.
[1] Early Training (processing week, training week 1 thru 4), Late Training (training week 5 thru 12) .
[2] Core body temperature (Tre) < 103.1°F.
[3] Core body temperature (Tre) ≥ 103.1°F.

A second model using only the cases and matched controls from late training, also included BMI and initial run-time, to which was added a term for the percent improvement in the run-times between training weeks 1 and 5. Both BMI and initial run-time were important predictors for overall, mild and severe EHI in early training. However, in late training, the initial BMI was no longer as important a risk factor. Here, body mass index appeared to exhibit a protective effect, but due to the wide confidence interval one does not want to over interpret these results. Also, misclassification of training period could partially explain this observation. The initial run-time remained a strong predictor of all, mild and severe EHI risk in late training. Additionally, the improvement in run-time was an important predictor of decreased risk.

To identify specific subgroups of marine recruits at risk of mild EHI, models were stratified by gender and categories of BMI (Table 3.13) and WBGT (Table 3.14).

Table 3.13. Models for mild EHI risk among male and female Marine recruits by categories of BMI.

Model	BMI (kg/m^2)	BMI Category	Risk Factor	Males Odds Ratio* (95% CI)	Females Odds Ratio* (95% CI)
1	Males ≥ 26 Females ≥ 23.4	High	Run	1.40 (1.09 – 1.79)	2.11 (0.50 – 8.91)
2	Males < 26 to 22 Females < 23.4 to 19.8	Medium	Run	1.72 (1.39 – 2.14)	1.71 (0.67 – 4.39)
3	Males < 22 Females < 19.8	Low	Run	1.18 (0.64 – 2.17)	2.72 (0.44 – 16.7)

*Male cases/Controls; Model 1: 108/378, Model 2: 159/323, Model 3: 55/59.
Female cases/Controls; Model 1: 14/32, Model 2: 15/78, Model 3: 12/21.

Run-time was an important risk factor of mild EHI for male recruits with high and medium BMI, while the model was quite unstable for the women (Table 3.13). For weather conditions, run-time was an important risk factor of mild EHI for male recruits for green flag WBGT temperatures, as well as, those WBGT temperatures below established flag conditions for all recruits (Table 3.14).

Table 3.14. Models for mild EHI risk among male and female Marine recruits by WBGT flag conditions.

Model	WBGT (°F)	Flag Conditions	Risk Factor	Males Odds Ratio* (95% CI)	Females Odds Ratio* (95% CI)
1	< 80	Under	BMI	1.04 (0.98 – 1.11)	1.00 (0.71 – 1.42)
			Run	1.95 (1.57 – 2.42)	3.91 (1.39 – 11.0)
2	80 to 84.9	Green	BMI	1.10 (1.01 – 1.21)	0.76 (0.52 – 1.11)
			Run	1.24 (1.01 – 1.54)	0.39 (0.08 – 1.83)
3	85 to 87.9	Yellow	BMI	1.22 (1.01 – 1.48)	0.86 (0.49 – 1.53)
			Run	1.29 (0.81 – 2.06)	5.10 (0.39 – 66.3)
4	88 to 89.9	Red	BMI	1.71 (0.98 – 2.99)	-
			Run	0.35 (0.07 – 1.70)	-
5	≥ 90	Black	BMI	1.08 (0.77 – 1.50)	0.40 (0.09 – 1.70)
			Run	1.13 (0.51 – 2.49)	22.10 (0.74 – 10^5)

*Male cases/Controls; Model 1: 175/503, Model 2: 94/225, Model 3: 17/62, Model 4: 14/16, Model 5: 8/18.
Female cases/Controls; Model 1: 20/72, Model 2: 10/57, Model 3: 4/18, Model 4: 1/1, Model 5: 4/8.

While, BMI was found to increase risk of mild EHI for green and yellow flag conditions of WBGT 80 to 87.9°F (26.7 to 31.1°C) for male recruits. The effects of WBGT on risk of EHI are studied in more detail in the previous chapter.

Measures of Absolute Risks for EHI of Marine Recruits at Parris Island

A conditional categorical logistic model containing three categories of BMI and four categories of VO_{2max} was used to obtain parameter estimates from which table of absolute risks could be created for male recruits. A similar table was created containing only the four categories of VO_{2max} for female recruits (see methods). The absolute risks for male and female Marine recruits for all EHI severity are shown in Tables 3.15 and 3.16. For male recruits in the highest risk category (BMI $\geq$ 26 kg/m^2 and VO_{2max} < 40.98 ml/min·kg), the absolute risk was 4.8-cases/1000 male Marine recruits, while for the highest risk category (VO_{2max} < 32.72 ml/min·kg) for female recruits; the absolute risk was 8.6-cases/1000 female Marine recruits.

Table 3.15. Absolute risk, male cases per 1000 recruits.

$V O_2 MAX$ (ml/min·kg)*	**Low** Males ≥ 48.20	**0.7**	**0.5**	**0.4**
	Medium Males < 48.20 to 44.23	**1.2**	**0.8**	**0.7**
	Medium Low Males < 44.23 to 40.98	**2.8**	**2.0**	**1.5**
	Low Males ≤ 40.98	**4.8**	**3.4**	**2.7**
		High Males ≥ 26	**Medium** Males < 26 to 22	**Low** Males < 22
		BMI (kg/m^2)**		

*Estimated from ACSM Guideline Tables 1995.
**Gardner 1996.

Table 3.16. Absolute risk, female cases per 1000 recruits.

$V O_2 MAX$ (ml/min·kg)*	**High** ≥ 40.98	**1.2**
	Medium < 40.98 to 36.65	**2.9**
	Medium Low < 36.65 to33.76	**3.4**
	Low ≤ 33.76	**8.6**

*Estimated from ACSM Guideline Tables 1995.

This risk for male recruits was approximately twelve times that in the lowest risk category of BMI and VO_{2max} and for female recruits, the risk was 7 times that in the lowest risk category of VO_{2max}. Predicting risk using these tables requires knowledge of recruit height, weight, and initial run-time. From there, BMI and initial VO_{2max} are calculated.

DISCUSSION

Generally, cases were more likely to come into recruit training in poorer condition than controls with a lower estimated VO_{2max} and higher initial physical fitness test (PFT) run-time. Male cases also had a higher BMI, which is consistent with their poorer conditioning. Cases did worse in strength assessment, in that male cases did fewer pull-ups and sit-ups than their control counterparts and female cases held their pull-up extensions for shorter periods than female controls.

Overall, we found that initial PFT run-time was an important independent risk factor for developing exertional heat illness (EHI) during the 12 weeks of basic training at Marine Corps Recruit Depot, Parris Island (MCRD-PI) for all Marine recruits. BMI and initial 1.5-mi PFT run-time were both important independent risk factors for developing EHI during the 12 weeks of basic training at MCRD-PI for male Marine recruits, as was previously reported in a study by Gardner et al with a smaller cohort of male Marine recruits (9). For female recruits, the initial .75-mi PFT run-time alone was a strong predictor of developing EHI during basic training. The odds ratio for females was almost twice as large as it was for male recruits. However, BMI does not appear to be a risk factor for developing EHI for female recruits, as it was observed for male recruits, over the 12 weeks of basic training at MCRD-PI.

Another way that we examined gender differences was to compare estimated VO_{2max}. These models had the advantage that male and female recruits could be compared more directly, since the run-time comparisons were hampered by the fact that the distances run were different for men and women. Recruits who came into training in good fitness were at lower risk for developing EHI, probably because good aerobic fitness provides increased cardiac output, permitting greater blood flow to the skin and muscles needed for thermoregulation and exercise reducing the risk of EHI (1), (24). Maximal oxygen uptake per unit body mass (ml/min·kg), expressed as VO_{2max}, is the laboratory measure of aerobic fitness (14). Run-times have been found to correlate well with VO_{2max}, making them a good measure of cardiovascular fitness, and allowing one to estimate the latter from the former. We examined the level of cardiovascular fitness by using estimated VO_{2max} from initial PFT run-time, and found that both male and female recruits entered basic training with the same amount of cardiovascular conditioning. There was no gender difference in the magnitude of the effect of VO_{2max} on risk of EHI.

Race initially appeared to be an independent risk factor for EHI in male recruits, but when models of EHI risk using BMI and run-time (or VO_{2max}) were stratified by race, the effects of these two risk factors were similar between the race groups. Race also did not appear to be a confounder in this study, nor was race an effect modifier (model 3, Table 3.6) for EHI in this cohort of Marine recruits.

Our main objective was to determine if the effects of BMI, PFT run-times, and VO_{2max} on EHI differed by severity level. Stratifying EHI into mild and severe EHI using body core temperature measured in the field shortly after case occurrence, we found that the risk factors were more strongly related to severe EHI in male recruits than to mild EHI. The combined effects of BMI and initial 1.5-mi PFT run-time were found to be quite important in determining severe EHI risk in male recruits, while the effects of these risk factors were independent in predicting mild EHI risk in these same male recruits. There was a negative interaction between the BMI and run-time in predicting severe EHI, meaning that their combined effect was somewhat smaller than would be expected based on the independent effects of BMI and run-time separately. The differences in the predictors of risk of EHI for mild and severe cases could be a result of dehydration or some unknown pre-existing health condition compromising a recruit's thermoregulatory response to heat. Male and female recruits were observed to differ in the average severity of EHI cases, with 55% and 45% of male recruits classified as mild and severe respectively, compared to 83% and 17% of women, respectively. Male recruits may have had a higher risk of severe EHI since they were more likely to come into training overweight, as a consequence of a more lenient weight standard (Table 3.17) than female recruits.

Female recruits were found to become EHI cases at a lower body core temperature than male recruits with mean body core temperature of 101 vs 103°F (38.3 vs 39.4°C), respectively. Kark reported in a previous study of Marine recruits at MCRD-PI that 11% of male recruit EHI cases and no females recruit EHI cases were hospitalized for EHI (13). Our results support his findings that male recruits were at

greater risk of developing a more severe EHI requiring hospitalization, while female recruits were at greater risk of developing a less severe EHI with no hospitalization.

We found an additional increase in EHI for male recruits in late recruit training, so training was stratified into early and late training. Early training consisted of the initial week of processing plus the first four weeks of recruit training, up to and not including the second PFT run. Late training included the remaining eight weeks of recruit training. The late EHI cases occurred when most recruits were already conditioned from the previous five weeks of exercise and training.

In early training, BMI and initial PFT run were better predictors of EHI than when used to predict EHI risk over the entire period of basic training. This was true for both categories of male recruit EHI severity. Again, as mentioned above, the combined or joint effect of BMI and initial PFT run was extremely important in predicting severe EHI during early training. This was possibly the result of male recruits not coming into basic training in top physical shape, and EHI cases occurring during the weeks of initial recruit conditioning and acclimation.

In late training, BMI was not found to be as important a risk factor as in early training. This was possibly due to male recruits increased level of aerobic conditioning from the early training and loss of weight, reducing a recruit's BMI by this period in training. The initial PFT run-time remained an important independent risk factor for all categories of EHI occurring in the late training, although at a reduced level compared to models of early EHI risk. The degree of improvement in run-time from the first to fifth weeks was important in determining EHI risk in late training, over an above the risk from having a slow initial run-time. Percent run improvement was a very good predictor of reducing risk of EHI, primarily for severe EHI in male recruits. Risk of EHI, especially severe EHI remained elevated during the second half of training, by which time training should have resulted in excellent conditioning, and a low risk of EHI. This might be the result of recruits pushing their thermoregulatory thresholds past safe limits because of insufficient hydration or a combination of hydration and training activities, which could occur during the week of the "Crucible" (a rigorous 54-hour field training exercise consisting of forced marches, military exercises and sleep deprivation; requiring teamwork, problem solving and physical endurance) or other types of intense physical training that are compounded by hot weather conditions.

Female recruits appeared to enter basic training in better physical shape then male recruits as indicated by the smaller female BMI coefficient of variation (COV -- 8.64) compared to the male COV (13.24). The fact that BMI was a risk factor in males but not in females may be explained by this lower variability in female BMI on entry. The narrower range of BMI in females may, in turn, be the result of a disparity in induction standards for male and female recruits. Male recruits entering MCRD-PI were allowed a higher maximal BMI 27.6 kg/m2 (Table 3.17) compared to female recruits, who's acceptable maximal BMI, was 25.3 kg/m2 (25). Surprisingly, according to the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (18), the upper bound of the acceptable range for male recruits falls

just below the classification "obese", while the upper bound of the female recruit standards come under the classification of "slightly overweight", but not obese. These lower weight standards for female recruits most likely screen out heavier women who otherwise would be at high risk of EHI. Another plausible explanation was that only physically fit and motivated women entered MCRD-PI basic training.

The difference in EHI risk by run-time in male and female recruits may have been at least partially explained by gender differences in sweating rates (2-3). Unconditioned women have been found to have higher body core temperatures when compared to unconditioned men due to their reduced sweating rate, which may partly explain their higher risk of EHI during the initial PFT run. On the other hand, in our study, female recruit EHI cases were found to have a lower body core temperature than male recruit cases – the opposite of what one might expect from the above observations on sweating in unconditioned men and women. This lower body core temperature may have been due to a shorter initial PFT run distance, or possibly these unconditioned female recruits were more sensitive to EHI at a lower body core temperature than male recruits. Without further data, it is difficult to make any further inferences about the differences in body core temperatures of male and female cases.

Women presented with the same demand as men have also been found to have a lower maximal aerobic capacity when compared to men resulting in an increased workload with higher body core temperatures than men (21-22). The previous described stricter BMI standard for female recruits perhaps provides these female recruits with less strain on their aerobic capacity, which may partially explain their reduced overall risk of EHI.

As mentioned above, we compared male and female recruit conditioning by using the estimated $V0_{2max}$. Using $V0_{2max}$ as a predictor, we found the risk for EHI between male and female recruits to be approximately the same per unit of oxygen consumed. In these models, BMI continued to only be a risk factor for male recruits. This finding reinforces our observation that women tend to enter recruit training in better condition than the men, since un-acclimated women in general have been found to have a reduced $V0_{2max}$ capability when compared to men, which should lead to an increased EHI risk, if selected under the same set of standards as the men. These female recruits, on the other hand, had the same incremental risk of EHI per unit of oxygen consumed as male recruits.

We were able to determine absolute risk of EHI for this recruit population because models using the risk factors of BMI and initial PFT run-time fit EHI risk quite well. We therefore developed prediction tables of EHI for this population of Marine recruits during basic training at MCRD-PI. The application of these tables will be discussed in the final chapter of overall conclusions.

Advantages of this study were: 1) the ability to control for the primary risk factors for EHI: climate, physical exertion, training conditions, and clothing by matching on initial training platoon, 2) all recruits experienced the same medical testing, given the

same nutritional regime, and were not allowed to use alcohol or tobacco products, which eliminated potential confounding from these variables, 3) having a larger number of cases and controls than a previous Marine recruit training study, 4) females, although few, still could be studied for risk of EHI during basic training, and 5) having EHI case body core temperatures allowing us to classify EHI into two categories of mild and severe categories.

Disadvantages of this study were 1) weather conditions were not considered as a risk factor of EHI; however, the wet bulb globe temperature (WBGT) and its component temperatures are examined in Chapter 2, 2) only two variables were found that could predict EHI risk reasonably well, and 3) the small number of female recruits, making it difficult to directly compare male and female recruits.

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CHAPTER 4: HEAT ILLNESS MORTALITY STUDY

INTRODUCTION

Evidence from the literature suggests that severe heat illness may cause irreversible acute damage to the heart, lungs, kidney and liver, which could lead to cardiovascular disease (CVD), ischemic heart disease (IHD), chronic liver or pulmonary disease, and/or renal failure. In particular, heatstroke is known to cause damage to tissue of the heart, kidney and liver (4-5), (11), (15).

Whether the compromising of one or more organ systems through over-heating leads to reduced heat tolerance during future high heat exposures is not known. If it were so, then an individual could be at higher risk of developing chronic heart, pulmonary, kidney and/or liver diseases that could eventually prove fatal. It is also possible that survivors of an acute heat illness suffer increased risk of mortality because of mild but irreversible damage to the circulatory system, which over time increases their susceptibility to other cardiovascular risk factors. Some chronic effects from exposure to heat stress have been suggested by experimental and epidemiologic evidence (2), (13-14). Documented evidence of life-threatening arrhythmia and other serious cardiovascular events have been observed in a population of US Marine recruits who have suffered heat illness (9-10). There is also some evidence of excess or heat-related ischemic heart disease, cardiovascular disease, and non-malignant digestive disease from studies of workers exposed to hot occupational environments (14), (18).

The objective of this study was to document the fatal sequelae of heat illness by following up a cohort of U.S. Army soldiers hospitalized for severe heat illnesses. It was hypothesized that severe heat illness, as evidenced by a history of hospitalization for heat illness would increase the risk of premature death due to cardiovascular disease, ischemic heart disease, chronic liver disease, or renal failure. To our knowledge, no such mortality follow up study has ever been conducted.

From the outset, it was clear that there were several substantial methodologic challenges to this investigation. First, the study had to rely on the Individual Patient Data System (IPDS) computerized Army medical records system to identify cases (8). This system has only been in place since 1971 and, because soldiers are typically 18 to 20 years old, it was clear that the study would be examining a relatively young cohort. Thus any conclusions would have to be considered tentative because there would be very little person-time of observation in the older years of life. The second important limitation of any study of a military population is that soldiers tend to be healthier than the general population, at least at entry into military service. We were aware, therefore, that it would not be appropriate to compare the mortality experience of soldiers who suffered a heat illness to the mortality experience of the general population because of this "healthy soldier effect". The solution was to choose a comparison population consisting of soldiers hospitalized for some other cause. But such cause-cause comparisons of risk create their own biases, if the comparison cause is itself related, even indirectly, to the exposure (heat illness) of interest. We chose to use

hospitalization for appendicitis as the comparison cause, reasoning that this is as far as is known, an essentially random event which is severe enough to require hospitalization.

METHODS

A retrospective cohort design was conducted to examine mortality outcome over a 30-year period in a cohort of U.S. Army soldiers hospitalized for heat illness (cases) and (comparison group). Overall and cause-specific mortality data were obtained by linking social security numbers (SSN) to the Defense Manpower Data Center (DMDC) and National Death Index (NDI) death files. Statistical methods included direct age standardization and Cox regression models of the follow up of mortality risk among Total Army Injury and Health Outcomes Database (TAIHOD) heat illness cases compared with the referent conditions.

Study Population

Subjects were drawn from all U.S. Army officer and enlisted active duty personnel hospitalized from 1971 to 2000. Cases of heat illness and of the comparison cause were identified through the TAIHOD database, maintained at the U.S. Army Research Institute of Environmental Medicine in Natick, MA.

Index cases were all heat illness (ICD-9 code 992) hospitalized in a U.S. military hospital and recorded in the TAIHOD database from 1971 to 2000 (1). Comparison subjects were U.S. Army soldiers hospitalized for appendicitis (ICD-9 codes 540-542) without ever having an episode of heat illness during their military career.

First, a list was extracted from TAIHOD containing only the SSNs of individuals hospitalized for heat illness or appendicitis. These bare SSNs were sent to the Defense Manpower Data Center (DMDC) in Monterey, CA. DMDC applied their Social Security Administration (SSA) files to determine which of the previously hospitalized individuals had died during the 30-year follow-up period of the study.

The DMDC and TAIHOD files do not provide cause of death, so it was necessary to send the SSNs, first and last name, date of birth, date of death, and gender of the known deaths to the National Death Index (NDI) in Hyattsville, MD, where individual causes of death data were extracted. Since the NDI files do not go back before calendar year 1980, deaths that occurred before 1980 were excluded from the NDI search. The cause of death data were then merged with the Army death data, the hospital data, and demographic data from TAIHOD DMDC files. A final working dataset was created by linking all relevant variables from each source file. The file contained a subject ID, which replaced the SSN returned with the death data from the DMDC or NCHS, leaving no personal identifiers in the final analytic dataset. This study was approved by the Scientific and Human Use Internal Review Board at USARIEM.

Outcome Variables

The outcomes of interest were overall and cause-specific mortality. Immediate and underlying causes of death recorded in the National Death Index (NDI)[i,ii,iii] were extracted. Cause-specific death categories of interest were *major cardiovascular disease* (ICD-9 codes 390-448), *ischemic heart disease* (ICD-9 code; 410-414), *chronic liver disease* excluding *cirrhosis* (ICD-9 codes 571.4-573.9), and *renal failure* (ICD-9 codes 584-586).

Exposure and Other Covariates

The principal contrast of interest was that between hospitalization for heat illness and for appendicitis. In addition, the state in which the patient died, as recorded in the NDI, was used as a proxy for post-military exposures to heat. States were grouped into two regions to represent differences in US regional seasonal climates. Age was considered a potential confounder and all rates were age-standardized (see below). Gender and race were treated as potential effect modifiers.

Analytical Methods

Overall and cause-specific mortality rates were calculated by 5-year-age groups. Standardized rate ratios (SRR) were computed for overall and cause-specific mortality outcomes using the person-years distribution of the appendicitis patients as the standard. This permitted direct comparison of mortality rates within each category by applying the age-specific rates of the appendicitis cases to the age distribution of the heat illness group (3).

The overall mortality and cause specific mortality of the heat illness cohort was also compared to the mortality experienced by the United States population using the U.S. population as the standard (1991) (12), (17). As noted above, these comparisons were expected to be biased by a "healthy soldier effect", but it was still judged to be useful to observe the magnitude of this mortality differential.

Direct standardization produces unstable risk estimates when data are sparse, as in this cohort (3). A better approach is to fit the Cox proportional hazards model, using heat illness versus appendicitis as a dichotomous "exposure" variable. We fit these models using the PHREG procedure in SAS, investigating confounding and/or effect modification by gender, race and rank (enlisted/officer) (6), (16). The LIFEREG procedure was also used to create survival curves as a graphic check on the Cox proportional hazards regression models.

RESULTS

Characteristics of U.S. Army Hospitalized Subjects

Demographic characteristics of the two hospitalization groups are provided in Tables 4.1.

Table 4.1. Demographic characteristics of subjects diagnosed with heat illness and appendicitis.

	Subject Category	
	Heat Illness (n=3971)	**Appendicitis (n=17233)**
Demographics		
Year of DX, y (mean ± SD)	1985.8 ± 7.3	1982.0 ± 8.1
Age at DX, y (mean ± SD)	23.5 ± 5.5	24.5 ± 6.0
Age at end of follow-up, y (mean ± SD)	38.0 ± 7.8	42.64 ± 9.3
Length of follow-up, y (mean ± SD)	14.4 ± 7.2	18.2 ± 8.1
Gender, %		
Male	89.7	94.1
Female	10.3	5.9
Race, %		
White	70.3	77.7
African-American	22.1	16.3
Other*	7.6	6.0
Rank, %		
Enlisted	88.0	90.0
Officers**	11.3	8.7

*Includes all other races except white and African-American.
**Includes warrant officers, who constituted about 1% of cases.

Heat Illness (HI) subjects were about one year younger on average at the time of their hospitalization than the comparison appendicitis (APX) subjects (23.5 vs 24.5 years), and their age at end of follow-up was more than four years younger. Age at end of follow-up means age at death for cases, and age on December 31, 2000, when follow-up ceased. The time from diagnosis to end of follow-up was also shorter for HI subjects than for APX subjects. Males accounted for 89.7% of the HI cases and 94.1% of the APX cases. The racial distributions of HI and APX cases were similar, although HI cases tended to be somewhat more African-American (22% versus 16%). Most of the HI and APX cases (88% and 90%, respectively) were enlisted Army personnel. The remaining cases were made up of officers (10%). Warrant officers, who made up about 1% of cases, were combined with officers in all analyses.

Demographic characteristics of those who died in this cohort are provided in Table 4.2. There were 115 deaths among the HI case group, and 585 among the APX cases. The mean year of death for all causes occurred nearly two years earlier for APX then HI cases, but HI subjects on average died at a somewhat younger age than the referent group -- 37.1 vs 40.4 years. Most of the deaths occurred for those cases diagnosed before the age of 40 (97% HI and 92% APX). The majority of all deaths were males (96.5% HI and 98.3% APX). White subjects made up 67.5% and 78.9% of the deaths in the HI and APX groups, respectively.

Table 4.2. Demographic characteristics of deaths (from all causes) among those diagnosed with heat illness and appendicitis.

	Subject Category	
	Heat Illness (n=115)	**Appendicitis (n=585)**
Demographics		
Year of Death, y (mean ± SD)	1993.2 ± 5.5	1991.5 ± 5.9
Age at Death, y (mean ± SD)	37.1 ± 9.8	40.40 ± 11.5
Age at DX < 40, y	112	535
Gender, %		
Male	96.5	98.3
Female	3.5	1.7
Race, %		
White	67.5	78.9
African-American	24.6	18.9
Others*	7.9	2.2
Rank, %		
Enlisted	94.8	90.9
Officers	2.2	7.0
Warrant Officers	-	2.1
Region of U.S., %		
North	33.0	33.7
South	67.0	66.3

*Includes all other races except white and African-American.

For African-Americans the percentages were 24.6% and 18.9%, while all other races were 7.9% HI and 2.2% APX. Most of the deaths occurred in enlisted personnel – 94.8% HI and 90.9% APX. With the small numbers of deaths available, only broad cause of death categories could be examined (Table 4.2). The percentages of deaths due to circulatory, respiratory, digestive, external, other causes (all other), cardiovascular disease (CVD), ischemic heart disease (IHD), liver disease, and renal failure were similar between HI and APX cases, while those for neoplasms were higher for APX cases (Table 4.3).

Table 4.3. Causes of death among those diagnosed with heat illness and appendicitis.

	Subject Category	
Cause of death	**Heat Illness n (%)**	**Appendicitis n (%)**
All-Causes	115 (NA)	585 (NA)
Neoplasms[1]	10 (9%)	100 (17%)
Circulatory[2]	25 (22%)	129 (22%)
Respiratory[3]	1 (1%)	13 (2%)
Digestive[4]	8 (7%)	28 (5%)
External[5]	51 (44%)	228 (39%)
Other[6]	18 (15%)	86 (15%)
Unknown	2 (2%)	1 (0.2%)
Specific causes of a priori interest		
Cardiovascular Disease[7]	15 (13%)	80 (14%)
Ischemic Heart Disease[8]	8 (7%)	35 (6%)
Liver Disease[9]	2 (2%)	12 (2%)
Kidney Disease[10]	1 (1%)	2 (< 1%)

[1] Neoplasms: ICD-9 140-239; ICD-10 C00-D48.
[2] Circulatory: ICD-9 390-459; ICD-10 I00-I99.
[3] Respiratory: ICD-9 460-519; ICD-10 J00-J98.
[4] Digestive: ICD-9 520-579, 588-589; ICD-10 K00-K92.
[5] External: ICD-9 E800-E999; ICD-10 S00-Y89.
[6] Other: ICD-9 All others.
[7] Major cardiovascular disease (CVD): ICD-9 390-448; ICD-10 I000-I789.
[8] Ischemic heart disease (IHD): ICD-9 410-414; ICD-10 I200-I259.
[9] Chronic liver disease: ICD-9 5710-5719; ICD-10 K700-K769.
[10] Renal Failure: ICD-9 584-586, 588-589; ICD-10 N170-N189, N250-N289.

Age-specific all-cause mortality rates for males and females are shown in Tables 4.4 and 4.5 and Figures 4.1 and 4.2.

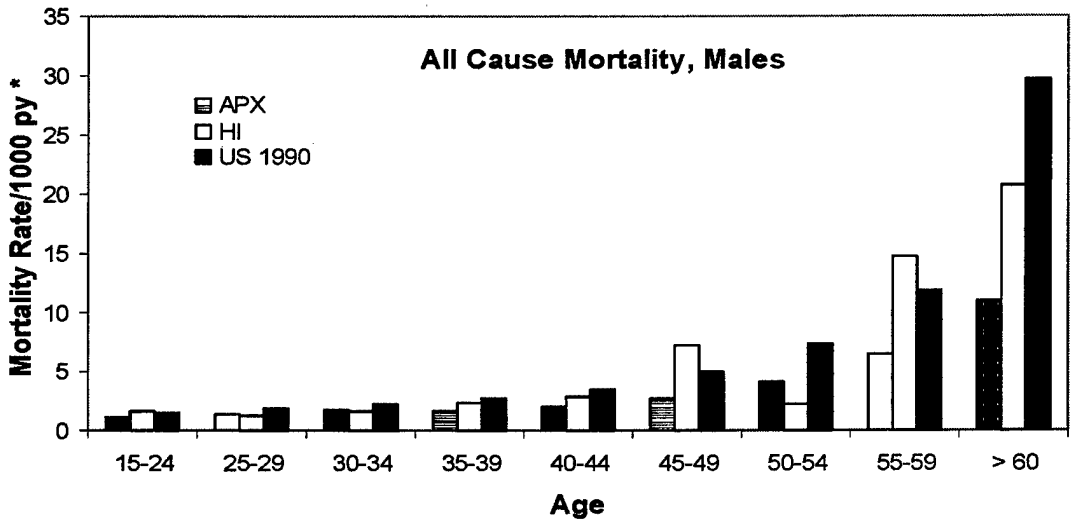
Table 4.4. Age-specific all-cause mortality rates for males. Comparing cohorts hospitalized for heat illness (HI) and appendicitis (APX).

Males: All Causes						
	Heat Illness			Appendicitis		
Age Groups	P-Yrs	Deaths	Death Rate per 1000 PY	P-Yrs	Deaths	Death Rate per 1000 PY
15-24	8380	14	1.7	31704	37	1.2
25-29	12460	15	1.2	55247	74	1.3
30-34	11956	19	1.6	58899	104	1.8
35-39	8555	20	2.3	53822	86	1.6
40-44	5316	15	2.8	42836	83	1.9
45-49	2620	19	7.3	26761	72	2.7

Males: All Causes						
	Heat Illness			Appendicitis		
Age Groups	P-Yrs	Deaths	Death Rate per 1000 PY	P-Yrs	Deaths	Death Rate per 1000 PY
50-54	871	2	2.3	11863	49	4.1
54-59	271	4	14.8	4960	32	6.5
≥ 60	145	3	20.2	3439	38	11.0
Total	50574	111	2.2	289531	575	2.0

There were four times as many subjects hospitalized for APX and they had a slightly lower crude all-cause mortality rate (2.0 vs 2.2) than HI subjects. The age-specific mortality rates were higher for men hospitalized for HI in 6 out of 9 of the age groups (Figure 4.1).

Figure 4.1. Age-specific mortality rates. Comparing cohorts hospitalized for heat illness (HI), appendicitis (APX) and U.S. 1990 population.



*Person-years

The all-cause death rates among those 45 to 49 and 55 to 59 were substantially higher for the HI than the APX group, and based on fairly large numbers of deaths. The pattern did not appear very different for women, although the numbers of deaths in age categories were very small (Table 4.5 and Figure 4.2).

Table 4.5. Age-specific all-cause mortality rates for females. Comparing cohorts hospitalized for heat illness (HI) and appendicitis (APX).

Females: All Causes						
	Heat Illness			Appendicitis		
Age Groups	P-Yrs	Deaths	Death Rate per 1000 PY	P-Yrs	Deaths	Death Rate per 1000 PY
15-24	1056	-	-	2016	-	-
25-29	1508	2	1.3	3546	3	0.8
30-34	1428	1	0.7	3652	2	0.5
35-39	762	1	1.3	3102	2	0.6
40-44	322	-	-	2004	-	-
45-49	118	-	-	828	2	2.4
50-54	41	-	-	245	1	4.1
54-59	7	-	-	59	-	-
≥ 60	7	-	-	25	-	-
Total	5249	4	0.8	15477	10	0.6

Figure 4.2. Age-specific Mortality Rates. Comparing cohorts hospitalized for heat illness (HI), appendicitis (APX) and U.S. 1990 population.

*Person-years

The directly age-standardized all-cause death rate among male HI cases was substantially higher than that for APX cases: 5.7 per 1000 person-years compared to 3.4 per 1000 person-years (Table 4.6). However, the U.S. standardized rates also show the reduced mortality of both groups of soldiers, compared to the general population. The standardized rate ratio (SRR) comparing all-cause mortality among male HI to APX cases was 1.4.

Table 4.6. Standardized mortality rates, all causes of death. Comparing cohorts hospitalized for heat illness (HI) and appendicitis (APX) and U.S. 1990 population (US).

All Causes						
	Males			Females		
Mortality Rate per 1000 PY	HI	APX	US	HI	APX	US
Crude Rate	2.2	2.0	7.2	0.8	0.6	1.7
US Standardized Rate*	5.7	3.4	7.2	0.4	0.7	1.7

*Standardized to 1990 U.S. population.

Despite this overall difference, the male all-cause death rate was higher for males hospitalized for HI in age groups 45 to 49 and 55 to 59 when compared to the male U.S. rates (Figure 4.1). The pattern was similar among females, although, as expected, mortality rates were generally lower. There were only 4 deaths to female HI cases and 10 to female APX cases.

Measures of Mortality Risk of Hospitalized Subjects

An initial Cox regression model was constructed to compare male all-cause mortality between HI and APX groups (model 1, Table 4.7).

Table 4.7. Cox proportional hazards models for risk of death among males. Comparing HI to APX subjects.

Model	Cause	Underlying/multiple*	Rate Ratio** (95% CI) (AGE[1] As Matching Variable)
1	All Causes	*underlying*	1.40 (1.14 – 1.71)
2	Neoplasms	*underlying*	0.92 (0.46 – 1.84)
3	Circulatory	*underlying*	1.83 (1.19 – 2.83)
4	Respiratory	*underlying*	0.86 (0.11 – 6.81)
5	Digestive	*underlying*	2.56 (1.54 – 5.69)
6	External	*underlying*	1.22 (0.90 – 1.67)
7	All Other	*underlying*	1.41 (0.83 – 2.38)

[1] Age at death or age at follow-up.
*Underlying and/or multiple cause.
**Ratio of mortality rates for HI to APX subjects.

The result was the same as the SRR calculated by direct standardization. Despite the small numbers of deaths, the confidence interval around the point estimate of 1.4 was relatively narrow (95% CI = 1.1 – 1.7). We also found HI cases to be at higher risk of death than APX cases from circulatory (RR=1.83) and digestive (RR=2.56) causes after investigating the major cause-specific categories of deaths (models 2 through 7, Table 4.7).

We attempted to narrow the focus to deaths that might plausibly be associated with organic damage from heat illness (Table 4.8).

Table 4.8. Cox proportional hazards models for risk of death among males. Comparing HI to APX subjects.

Model	Cause	Underlying/multiple*	Rate Ratio** (95% CI) (AGE[1] As Matching Variable)
1	All Causes	*underlying*	1.40 (1.14 – 1.71)
2	All Causes[2], excluding external	*underlying*	1.55 (1.18 – 2.04)
3	All Causes[3], excluding external	*underlying or multiple*	1.53 (1.15 – 2.03)
4	CVD	*underlying*	1.71 (0.98 – 2.99)
5	CVD	*underlying or multiple*	1.75 (1.21 – 2.51)
6	All Causes / Multiple CVD	*all causes – underlying, CVD - multiple*	1.71 (1.19 – 2.47)
7	Ischemic Heart Disease	*underlying*	2.23 (1.02 – 4.90)
8	Liver Disease	*underlying*	2.98 (1.17 – 7.60)
9	Liver Disease[4]	*underlying*	1.41 (0.31 – 6.37)
10	Heat Related[5]	*underlying*	1.84 (1.22 – 2.77)
11	Heat Related[5]	*underlying or multiple*	1.67 (1.18 – 2.35)

[1] Age at death or age at follow-up.
[2] All Causes excluding underlying external causes.
[3] All Causes excluding underlying and multiple external causes.
[4] Liver disease excluding alcohol related.
[5] Heat Related including CVD, liver (non-alcohol) and kidney deaths.
*Cause of death recorded as an underlying or multiple cause on the death certificate.
**Ratio of mortality rates for HI to APX subjects.

This could only be done for males, however, because there were only 4 female deaths among HI cases. Excluding underlying external causes did not substantially change the risk of all-cause mortality (RR=1.36 vs RR=1.40). Also, excluding all additional multiple external causes did not alter the effect (RR=1.37 vs RR=1.40). Cause-specific mortality among males from cardiovascular disease (CVD), ischemic heart disease (IHD) and liver disease were also elevated in the HI case group, compared to APX (Table 4.8).

Other underlying causes suspected to be associated with heat illness could not be explored because of small numbers. Mortality from CVD was somewhat more strongly associated with history of heat illness (RR = 1.7) than was all-cause mortality (RR = 1.4). CVD was investigated both as an underlying cause of death (model 4 in Table 4.8), as well as either an underlying or a multiple cause of death (model 5), and the results were essentially unchanged. We also evaluated risk of death from any underlying cause in which CVD was listed as a multiple cause (model 6), and again the rate ratio comparing HI to APX was similar. For deaths with IHD as the underlying cause, the risk of death for HI subjects was more than 2 times (RR=2.2) that of APX subjects (Table 4.8). Heat illness subject deaths from liver disease were found to be 3 times that of APX subjects (RR = 3.0). However, when alcoholic related deaths were excluded, the strong association of liver deaths disappeared. Deaths from CVD (including IHD), liver disease and renal failure were combined to create a category of potentially heat related deaths, and these were almost twice as frequent in the heat illness group compared to the appendicitis group (model 10). Adding deaths for which one or more multiple causes were in this heat related group reduced the rate ratio somewhat (model 11). All-cause mortality among women was elevated in heat illness cases compared to appendicitis cases, with the same rate ratio as among males, although the confidence interval was quite wide due to the very small number of cases (Table 4.9).

Table 4.9. Cox proportional hazards models for risk of death among females. Comparing HI to APX subjects.

Model	Cause of Death	Rate Ratio (95% CI) (AGE[1] As Matching Variable)
1	All Causes	1.36 (0.42 – 4.43)

[1] Age at death or age at follow-up.
[2] All Causes Excluding Primary External Causes.
[3] All Causes Excluding Primary and Underlying External Causes.

The potentially modifying role of race was investigated among men (Table 4.10). In these analyses, only white and African-American races were included in the analysis, since "other races" did not have sufficient numbers of death. These models were estimated from 75 HI deaths and 453 APX deaths for white males and 27 HI deaths and 106 APX deaths for African-American males.

Table 4.10. Survival models for risk of death for all causes among males, separately for whites and African-Americans.

Model	Race	HI/APX Deaths (n)	Risk Factor	Males* Rate Ratio (95% CI) (AGE[1] As Matching Variable)
1	Both	102/559	Diagnosis**	1.31 (1.06 – 1.62)
			Race: Afro vs white	1.40 (1.15 – 1.69)
2	White[2]	75/453	Diagnosis	1.39 (1.08 – 1.77)
3	African-American[3]	27/106	Diagnosis	1.48 (0.75 – 1.76)

[1] Age at death or age at follow-up.
[2] White male hospitalizations: HI=2472, APX=12215
[3] African-American male hospitalizations: HI=702, APX=2442
*Includes white and African-American.
**Heat illness (1) versus appendicitis (0).

African-American males had a 40% higher risk of all-cause mortality compared to white males (model 1, Table 4.8). The effect of heat illness was only slightly changed by adding race to the model (RR = 1.3 for diagnosis in model 1, Table 4.10, compared to RR = 1.4 in model 1 of Table 4.8). When race was used as a stratifying variable, there was little evidence of differential risk of mortality due to heat illness. It thus appears that race is neither a confounder nor an effect modifier of the association between heat illness and male all-cause mortality.

Officers were at substantially reduced risk (RR=0.41) of all-cause mortality compared to enlisted men (Table 4.11).

Table 4.11. Survival models for risk of death for all causes among males, separately for enlisted and officers*.

Model	Rank	HI/APX Deaths (n)	Risk Factor	Males Rate Ratio (95% CI) (AGE[1] As Matching Variable)
1	Both	111/575	Diagnosis**	1.40 (1.15 – 1.73)
			Rank: officers vs enlisted	0.42 (0.32 – 0.55)
2	Enlisted	105/523	Diagnosis	1.42 (1.15 – 1.75)
3	Officers*	6/52	Diagnosis	1.32 (0.56 – 3.13)

[1] Age at death or age at follow-up.
[2] Male enlisted hospitalizations: HI=3132, APX=14595.
[3] Male officer hospitalizations: HI=429, APX=1614.
*Includes Officers and Warrant Officers.
**Heat illness (1) versus appendicitis (0).

As with race, this did not appear to confound the heat illness effect, however. When the data were stratified by rank, there was little evidence for a differential effect of rank on

risk from heat illness. Male mortality by U.S. region of residence at the time of death was investigated to determine if subjects who lived in hotter climates might have higher all-cause mortality rates than those subjects who lived in cooler areas of the country. Region of death was divided into areas of "north" and "south", which were comprised of states in the upper and lower half of the U.S, excluding Alaska, Hawaii, and Puerto Rico. Risk for all-cause mortality was found to be similar for these two regions of the U.S. (Table 4.12).

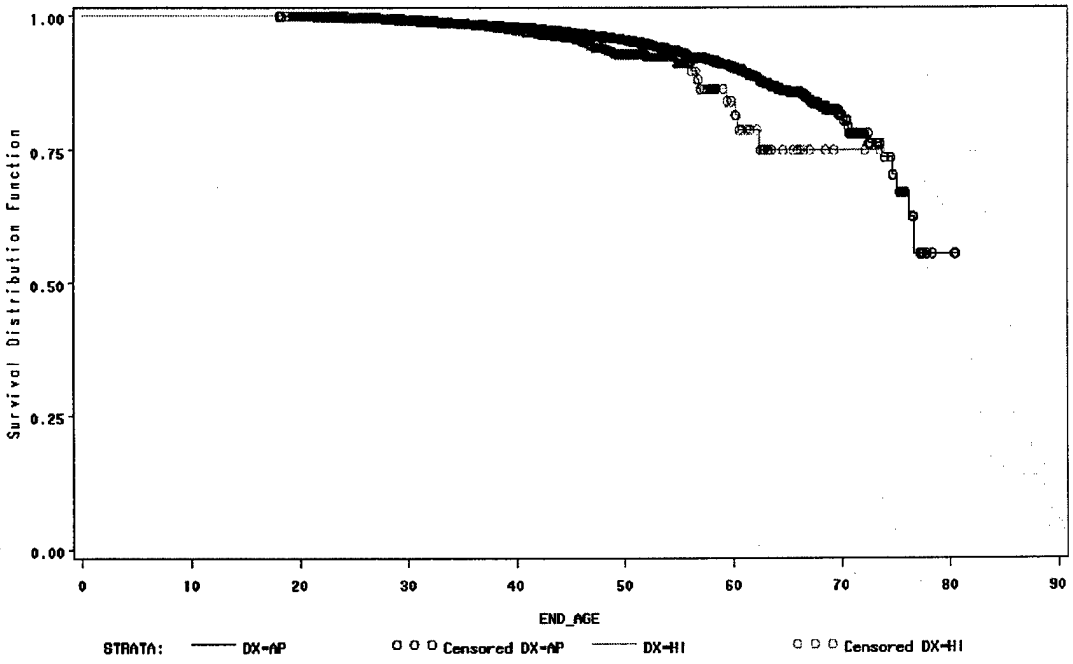
Table 4.12. Survival models for risk of death for all causes among males, separately for north and south regions of the U.S.

Model	Region	HI/APX Deaths (n)	Risk Factor	Males Rate Ratio (95% CI) (AGE[1] As Matching Variable)
1	North	37/191	Diagnosis	1.36 (0.95 – 1.94)
2	South	74/384	Diagnosis	1.41 (1.10 – 1.82)

[1] Age at death or age at follow-up.

Another way that all-cause death rates for HI and APX subjects were compared was by using survival curves (Figure 4.3).

Figure 4.3. Survival curves for all subjects hospitalized for heat illness[1,2] (HI) and appendicitis[1,2] (AP).



[1] Number of hospitalizations: HI=3970, APX=17233.
[2] Number of deaths: HI=115, APX=585.

The survival curves were quite similar up to age 35, at which point mean survival began to fall behind for HI subjects compared to APX cases. The two curves met again at approximately age 75, and the few deaths above this age appeared to have similar age distributions. These same patterns can be seen in the age-specific mortality rates in Tables 4.3 and 4.4.

DISCUSSION

This study demonstrated that both men and women who were hospitalized for a heat illness while in the Army experienced a 40% increased risk of all-cause mortality compared to a reference group of soldiers who had been hospitalized for appendicitis.

Age-specific all-cause mortality was especially high for male heat illness subjects in age groups 45 to 59 and 55 to 59, where the mortality rate was even higher than for the general U.S. population (Figure 4.1). The standardized rates for HI were consistently higher than APX among both males and females (Table 4.6). However, gender specific age standardized mortality rates for both HI and APX subjects were lower than those in the U.S. population. This was possibly the result of a "healthy soldier" effect, deriving from the fitness requirements for entry into the U.S. Army and the improved access to healthcare among soldiers, and to a lesser extent, among veterans as well. One would expect a biologic effect of heat illness to increase mortality from internal rather than external causes of death. The rate ratio associating heat illness with mortality was only slightly lower for internal causes versus all causes of death, which thus provides only modest evidence for a biologic explanation.

Further evidence was sought by restricting internal causes to those that are more plausibly related to organ damage following heat illness. For example, a prior severe HI episode might compromise the body's cooling mechanisms, resulting in excess stress on the heart, liver and kidneys. Hubbard reported that acute sequelae associated with heat illness consisted of mild to severe cardiovascular disturbances as well as evidence of cellular damage to tissues of the heart, liver and kidneys (7). Tissue and organ damage to the heart, liver and kidneys from heat stroke has been documented by Garcia-Rubira and others, which lead us to investigate these sites for a possible biological connection between increased mortality and HI hospitalization (5), (11), (15). The risk of cardiovascular disease (CVD) from heat illness among men was somewhat higher than the risk of all-cause mortality, although the rate ratio was less precisely estimated, due to the smaller numbers of deaths (see Table 4.8). Restricting cases to the subgroup of ischemic heart disease (IHD) deaths, the association with heat illness was further strengthened. This finding supports an earlier study by Kark et al, who found a very strong association between risk of life-threatening arrhythmias and heatstroke (10). It is also somewhat supported by an occupational study by Wild, who found a strong association between exposure to heat and IHD mortality (18). The risk of death from liver disease in HI subjects was found to be 3 times that of APX subjects, but when alcohol related deaths were excluded, the rate was greatly reduced. These rates for categories of death more likely to be associated with organ damage from heat illness were somewhat higher than those of all-cause mortality (Table 4.8), which lends support to a biologic explanation for the observed elevated risks of death.

Race appeared to be a strong independent risk factor for all-cause mortality in males but race was neither a confounder nor an effect modifier of the heat illness effect. Rank was also not a confounder or an effect modifier.

A cohort of healthy Army soldiers and veterans cannot be easily defined. As a result, it was necessary to compare the mortality experience of heat illness cases to that of another group of soldiers who experienced hospitalization. Nor was it valid to use the U.S. general population as a comparison group. Indeed, this study found that both heat illness and appendicitis cases were at substantially reduced risk of mortality compared to the general population. Because of these methodologic limitations, it must be remembered that all "effects" of heat illness on mortality are really differences in the mortality experience of heat illness and appendicitis cases. If the mortality experience of appendicitis cases is not representative of the general U.S. Army population, then these comparisons will be biased. We are not aware of reasons why this would occur, and we therefore believe that appendicitis is a reasonable reference cause of hospitalization. Other investigators have also used appendicitis in a similar manner (TAIHOD manuscript waiting approval). Nevertheless, the use of a reference cause of hospitalization remains a limitation of this study.

It is possible that there are other mortality risk factors associated with heat illness hospitalization, which are the real cause of the elevated risk of mortality among this cohort. Unfortunately, we did not have access to data on the lives of our subjects after their hospitalizations – information on other important risk factors like nutrition, occupation, utilization of medical care, smoking, high blood pressure, cholesterol and alcohol consumption.

To our knowledge, this was the first study of mortality following heat illness among military personnel. It benefited from the availability of a centralized health database for Army personnel (TAIHOD), which allowed us to identify cases and to construct a comparison population. Despite the small numbers, we were able to investigate females as well as males, and to show, that for all-cause mortality, their risk does not appear to be substantially different from that of males.

There were limitations, as well. The study was still rather small, and did not allow investigation of detailed causes of death. We lacked detailed information on the severity of the heat illness, the setting in which it occurred, and the course of treatment during hospitalization. The problem of the comparison population, and the lack of potentially important confounder information have been discussed. These findings are also limited because the cohort that we followed is still quite young – the average age of death was 37 years. Additional follow-up will be important to understand the risks in later life for those who suffered a heat illness.

In conclusion, in the first follow-up study of U.S. Army personnel who experienced a hospitalization for heat illness, we observed a 40% elevated risk of all-cause mortality. The risk was higher when the analysis was restricted to internal causes of death that

are plausibly related to organ damage following heat illness. Additional studies are warranted to understand if this potentially serious mortality risk can be shown to be causally related to the sequelae of heat illness.

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CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

CUMULATIVE HEAT EXPOSURE AND RISK OF HEAT ILLNESS

The wet bulb globe temperature (WBGT) heat index has been the "gold standard" used by both the U.S. Marines and U.S. Army as a tool to prevent the incidence of exertional heat illness (EHI) from environmental conditions during training and military operations. A system of warning flags was devised, based on the current WBGT, to provide guidance on the level of physical activity that was considered safe. This system has been used since the mid 1950's and was based on the training activities that were carried out during that period.

Over the years, training methods have changed, adding such things as timed running and higher levels of physical activities. Our study suggests that the WBGT, and the warning flags based on it, are no longer adequate for effective prevention of EHI. Perhaps the most compelling evidence of this is the observation that a majority of EHI cases (52%), occurred under presumably safe flag conditions of WBGT < 80°F (26.7°C).

The WBGT is a weighted average of three temperatures: the natural wet bulb (T_{nwb}), black globe (T_{bg}), and ambient (T_a) temperatures. Seventy percent of the weighting is given to the T_{nwb}, while the other two temperatures contribute the remaining 30%. Our investigations observed a very different pattern of relative importance. We found the ambient temperature, T_a, to be the most important of the three temperatures, and the T_{nwb} relatively less important. For example, we found that a two-temperature index predicted EHI risk somewhat better than WBGT, with components of T_a (61%) and T_{nwb} (39%). This new index, which we call the wet bulb dry temperature (WBDT) not only predicted risk better than WBGT, but it is also easier to compute, since the black globe temperature, T_{bg}, is not used.

We also found that an index using the percent relative humidity, where %RH was substituted in place of the natural wet bulb temperature predicted risk of EHI better than WBGT. This index, termed "the relative humidity dry temperature" (RHDT) index, is based on only the %RH and T_a. As with the WBDT, the RHDT is easier to calculate and has the advantage of not requiring the use of either the T_{nwb} or the T_{bg}. These studies suggest that the WBDT and RHDT may be better adapted to predicting risk of EHI for current training activities than is the WBGT. It is possible that the greater weight given to ambient temperature in the new indices reflects changes in heat load that have been brought about by the changes in training methods over the years. Alternatively, the fitness and conditioning of recruits may have changed in ways that reduce the importance of wet bulb temperature, or relative humidity, as a risk factor, and increase the importance of simple ambient temperature. More research will be needed to understand what might underlie these changes in the relative importance of the different aspects of hot climates for EHI risk.

Another area of concern, arising from the observation that a majority of EHI cases occurred under "safe" conditions, is the possibility of cumulative effects of prior days of heat exposure on risk of EHI. Kark et al (1996) found EHI rates to have a 26 and 39-fold increase at WBGT of 75°F to < 80°F (26.7°C), compared to baseline EHI rates at < 65°F (18.3°C), for immediate day and previous day exposures that occurred well below established flag conditions of ≥ 80°F (26.7°C) (7). They also reported that 87% of heat illness cases had been exposed to previous day WBGT readings above 80°F (26.7°C), pointing to a possible cumulative effect of heat exposure. Our results support these findings and suggest that the combined effect of current day and previous day WBGT is more important in predicting risk of EHI than current day WBGT alone. This cumulative effect appeared to be short-lived – the WBGT two days before training was not associated with EHI risk. We also found that previous day peak WBGT and average levels were equally good at predicting risk.

Combining what we have learned from developing new heat indices with what we know of the effects of cumulative heat exposure will allow us to better predict risk of EHI. This can be accomplished by applying the new heat indices of WBDT and RHDT formulated in this study to models containing current and previous day mean to better predict the risk of EHI in these Marine recruits.

EXERTIONAL HEAT ILLNESS SEVERITY PREDICTORS

Overall, it appears that initial physical fitness (PFT) run-time is a very good predictor of EHI risk for all Marine recruits in basic training at Marine Corps Recruit Depot, Parris Island, SC (MCRD-PI). Men also appeared to enter training in poorer shape then women recruits, at least using as the fitness criterion the body mass index (BMI). Body mass index was found to be a predictor of EHI risk in males, but not females, and we believe this is due, at least in part, to the considerably narrower range of BMI at entry among females than among males. Body mass index at entry for some males was sufficiently high, increasing their risk of EHI, while there were very few female recruits with BMIs high enough to confer EHI risk.

Our study supports the Gardner et al (1996) finding of a strong association between BMI and initial PFT run-time and EHI risk, in a study of a subset of this cohort of male Marine recruits (4). Gardner reported that recruits with a BMI of ≥ 22 kg/m^2 and a 1.5 mile run-time of ≥ 12 minutes had an 8-fold higher risk for developing EHI during basic training when compared with those recruits with BMI less than 22 kg/m^2 and 1.5 mile run-time under 10 min ($p < .001$). Our results suggest that a number of males who enter MRDC-PI are not in proper physical and/or aerobic conditioning to begin the grueling events of training often referred to as Marine Corps "Boot Camp". To reinforce our observation that women enter recruit training in better condition than the men, we compared male and female recruit conditioning using the estimated $V0_{2max}$. This measure was calculated using separate prediction equations for males and females, and was based on their individual initial PFT run-times. It appeared that the recruits' estimated oxygen consumption was a good predictor of aerobic fitness and risk of EHI for all recruits, regardless of gender. Also, the risk for EHI between male and female recruits was found to be approximately the same per unit of oxygen consumed.

Calculating a recruit's aerobic capacity after the initial PFT run may help in better assessing those individuals who are at high risk of EHI during training.

Our study cohort allowed us the unique opportunity of investigating the risk of EHI separately for mild and severe cases of EHI, since we had measures of body core temperature (T_{re}) collected in the field, shortly after the soldier became symptomatic. Mild EHI was defined as having a core body temperature below 103.1°F (39.5°C), while severe cases were those with core body temperatures above this cutoff. We determined that a number of risk factors were more strongly related to severe EHI in male recruits than to mild EHI. The effects of BMI and initial 1.5-mi PFT run-time appeared to be better predictors of severe EHI risk in male recruits with a somewhat lesser ability to predict mild EHI risk. BMI and run-time were found to be independent risk factors for mild EHI, while for severe EHI, there was in interaction between these two factors such that their combined effect was somewhat less than would be expected from the sum of their individual effects. It is difficult without medical data on mild and severe cases to speculate on why there might be differences in risk factors.

Very few women were identified as severe EHI cases in this cohort of recruits. This is possibly due to the differences in the male and female training regimens, in addition to differences in conditioning and selection criteria at entry. Severe EHI cases made up 55% of all male EHI cases, while only 17% of all female EHI cases were severe. The difference in severity by gender is also supported by a study done by Kark et al (1996), where they reported that 11% of male recruit EHI cases and no females recruit EHI cases were hospitalized for EHI during the years of 1982 to 1991 (6). This difference in EHI severity by gender might be the result of a disparity in weight standards and training or earlier intervention with female trainees who begin to show signs of heat illness.

Predictors of EHI risk apparently differ between early and late phases of the 12-week Marine training program. In early training, BMI and initial PFT run appear to be better predictors of EHI than when used to predict EHI risk over the entire period of basic training. This holds true for both categories of male recruit EHI severity. Again, the combined or joint effect of BMI and initial PFT run was very important in predicting severe EHI during early training.

Body mass index (measured at the start of training) appeared not to be as important a risk factor in late training as in early training, which is possibly due to weight loss and the increased level of aerobic conditioning attained from early training. We did not have access to a BMI calculated later in training. Unlike initial BMI, the initial PFT run-time continued to be an important independent risk factor for all categories of EHI occurring late in training, although at somewhat reduced strength compared to models of early EHI risk. The amount of improvement in run-time from the first to fifth weeks was found to be a key determinant in assessing EHI risk in late training, above and beyond the risk from having a slow initial run-time. Percent run improvement appeared to be a very good predictor of reducing risk of EHI, most notably for severe EHI in male recruits. After 5 weeks, one would hope that risk of EHI, especially severe EHI, should

be lower as a result of previous conditioning. Unfortunately, a substantial fraction of cases occurred after this date. This may be the result of more intense training activities and longer road marches carrying heavy packs that are compounded by hot weather conditions. These more severe stresses may not be adequately prepared for by the initial period of training.

As noted above, our data suggest that female recruits entered basic training in better physical shape then male recruits. A narrower range of BMI used in selecting female recruits may be resulting in a disparity in selection of male and female recruits. The lower weight standards for female recruits in all probability screen out heavier women who otherwise would be at high risk of EHI.

Female recruits also appear to have a higher risk of EHI than male recruits based on run-time alone. This difference in EHI risk by run-time in male and female recruits may have been at least partially explained by gender differences in sweating rates (2-3).

HEAT ILLNESS MORTALITY

It has been known, since the 1940's, that heat illness, especially severe heat illness, causes tissue and organ damage to the heart, liver and kidneys (8). Up to now, there have been no studies that have examined heat illness and its long-term effects on mortality. We were given the opportunity to investigate the risk of death in a cohort of U.S. Army soldiers who were previously hospitalized for heat illness and appendicitis. It appears that Army hospitalized male heat illness (HI) cases experience a 40% increase in risk of all cause deaths compared to referent (appendicitis, APX) cases. Women hospitalized for HI also appear to be at a similar elevated risk of all-cause mortality, but the risk estimate is much less precise because of the small numbers of female cases.

Age-specific all-cause mortality appeared to be especially high for male heat illness subjects in age groups 45 to 59 and 55 to 59, and for females in age groups 25 to 29 and 35 to 39, when the mortality rates were even higher than those of the general U.S. population. However, we cannot explain this finding at the present time. Age and gender specific mortality rates for both HI and APX subjects were lower than those in the U.S. population. This was possibly due to a "healthy soldier" effect, where people in poor health were most likely rejected after physical exam screening, permitting only healthy individuals to enter military service. Also, U.S. Army personnel have access to better health care than many members of the general population.

The elevated risk of death among HI cases was also observed when deaths were restricted to internal causes. The association was strengthened when analyses were restricted to deaths from cardiovascular disease (CVD), ischemic heart disease (IHD), as well as to a group of causes that could plausibly be associated with the long-term sequelae of heat illness. This group included CVD, liver and kidney diseases. For these heat-postulated related diseases, the risk of death was almost twice as high among HI cases as among the comparison group of appendicitis cases. Our results support an earlier study by Kark et al, which found a very strong association between risk of life-threatening arrhythmias and heatstroke (7). Death from liver disease in HI

subjects occurred almost 3 times as frequently as among the APX subjects, although effects of alcohol cannot be ruled out. Hubbard earlier reported that acute sequalae associated with heat illness consisted of mild to severe cardiovascular disturbances to evidence of severe cellular damage involving the heart, liver and kidneys, although acute, somewhat supports our findings of a potential biological effect (5).

Race appeared to be a strong predictor of risk of all-cause mortality in this cohort. African-American males were about 40% more likely to die than white males. Being an officer, compared to an enlisted man, appeared to confer strong protection against all-cause mortality. But despite these strong direct effects of race and rank on risk of death, neither was found to modify or confound the effect of heat illness on mortality. It also did not appear that all-cause mortality rates following HI hospitalization differed between the southern and northern U.S., even though those living in the south were more likely exposed to higher ambient temperatures after their military experience ended.

CONCLUSIONS AND RECOMMENDATIONS

Exertional heat injury (EHI) continues to occur with regularity during the training of Marine recruits at Marine Corps Recruit Depot, Parris Island (MCRD-PI). Environmental, personal and physical factors were found to contribute to risk of EHI during the 12 weeks of basic training of these Marine recruits. Exposure to heat, measured by hourly WBGT, was found to be a strong predictor of EHI risk. Our alternative indices, WBDT and RHDT, were found to predict risk of EHI somewhat better then the currently used WBGT. Also, we found the previous day's mean WBGT to be a strong predictor of EHI risk, over and above the effect of the current hourly WBGT. These findings provide strong evidence of a cumulative effect of heat exposure. In future work, we will apply our newly-developed WBDT and RHDT indexes to current day and previous day heat exposures to further investigate the cumulative heat effects of risk of EHI than the WBGT.

Body mass index (BMI) was found to be strongly associated with EHI risk in males, but not females. We mentioned a number of possible explanations in the discussion section of Chapter 3 and above relating to a disparity in selection criteria, especially with regard to weight standards. We believe that it is likely that women, if selected under the same induction standards as men, would demonstrate the same strong association between BMI and risk of EHI. And, the opposite would be true for males if selected under the female recruit induction criteria. Initial physical fitness test (PFT) run-time was also found to be a strong predictor for both male and female recruits, but again a difference in EHI risk exists. One possible explanation for male-female differences are gender differences in sweating rates. The lower sweating rates of unacclimatized women tends to result in higher body core temperatures (T_{re}) then unacclimatized men, but this was not observed in this cohort of female recruits. In fact, these female recruits had a *lower* T_{re} then male recruits possibly due to a more sensitive awareness of their condition than male recruits, resulting in a higher incidence of EHI. This difference in risk might disappear if male and female recruits were compared later in training – perhaps at the 2nd or 3rd PFT run, since it is well documented that T_{re} does

not differ for acclimatized men and women (1), (10). We were not able to make this comparison because the number of female recruits with 2nd and 3rd PFT run-times was too small.

Predictors of EHI risk were found to differ for severe and mild EHI for male recruits. Body mass index and run-time were found to be strong independent risk factors for all and for mild EHI, while the combined effect of BMI and run-time was more important in predicting risk of severe EHI. This difference in risk most likely exists because severe EHI is a further stage of mild EHI where all of the body's "cooling mechanisms" have shut down. It is plausible that this state is influenced by the interaction of BMI (fitness) and run-time (conditioning) than by either BMI or run-time alone.

What happens to these heat illness cases later in life? Do they continue to live normal lives or are they at higher risk of mortality because of residual effects of the organ damage they may have suffered? As we have seen, this study found evidence of increased risk of death among those hospitalized for heat illness. With the data available to us, it is not possible to make strong conclusions about this finding. We cannot exclude the possibility that there is some other systematic difference between heat illness and appendicitis cases which results in elevated mortality of the former compared to the latter group. We also cannot exclude the possibility that risk of heat illness and risk of premature mortality are both the result of some early life or even genetic risk factor.

In the near future, we hope to acquire additional cause of death information from both the National Death Index (NDI) and state death registries to increase the size of our outcome to further strengthen the results we have found in this study on mortality. Also, additional parameters such as length of military service (LOS) will be examined to see if LOS in some way effects survival of these hospitalized cases.

Weather training guidelines have been in effect since the mid 1950's when Dr. Minard instituted a WBGT index to help reduce the number of heat illness cases that occurred during training (9). These same training guidelines based on the WBGT are still currently in use today. Our findings suggest that these weather guidelines need to be updated. Training in the 1950's consisted of marching and calisthenics, and perhaps the WBGT and the flag system provided adequate protection during this kind of training. However, today's military training consists of timed runs and more intense training activities, which in turn, change the interaction between soldier and environment. We found ambient temperature (T_a) to be a much more important predictor of EHI risk than its weight in WBGT (10%) reflects. This might be one reason for the increased risk of EHI below established flag conditions. We recommend that consideration be given to applying one of the heat indices – WBDT or RHDT, in hot weather training conditions at Marine Corps Recruit Depot training at Parris Island, SC. Whether these indices are relevant to locations and weather patterns in other locales besides Parris Island is not known. We also recommend that consideration be given to the importance of cumulative heat effects. Our table (Table 5.1) illustrates these effects by showing the

risk (odds ratio) of EHI for combinations of current day and previous day average WBGT.

Table 5.1. Cumulative effects of heat on EHI risk: odds ratios for combinations of current hour and previous day average WBGT*.

Odds Ratio of EHI Risk										
Current Day WBGT (°F)	100	3.4	3.6	3.9	4.2	4.5	4.8	5.1	5.5	5.9
	95	2.9	3.1	3.3	3.5	3.8	4.0	4.3	4.6	4.9
	90	2.5	2.7	2.8	3.0	3.2	3.4	3.6	3.9	4.1
	85	2.1	2.3	2.4	2.5	2.7	2.9	3.0	3.2	3.4
	80	1.8	1.9	2.0	2.2	2.3	2.4	2.6	2.7	2.9
	75	1.6	1.7	1.7	1.8	1.9	2.0	2.1	2.3	2.4
	70	1.3	1.4	1.5	1.6	1.6	1.7	1.8	1.9	2.0
	65	1.2	1.2	1.3	1.3	1.4	1.4	1.5	1.6	1.7
	60	1.0	1.0	1.1	1.1	1.2	1.2	1.3	1.3	1.4
		60	65	70	75	80	85	90	95	100
		Previous Day Average WBGT* (°F)								

*Average of the hours from 7:00 am to 4:00 pm.
Odds ratio of 2.0 – 2.9.
Odds ratio of 3.0 – 3.9.
Odds ratio of $\geq$ 4.0.

Such a table might be used in a new flag system to identify hazardous training conditions.

As mentioned above, BMI and VO_{2max} were found to be strong predictors of EHI risk. These can be combined to yield risks of EHI for individual male recruits, while VO_{2max} can be used in this same manner to predict EHI risk for individual female recruits. Our Tables 3.14. and 3.16 presents data on the absolute risks of EHI, and could be used as a guide for identifying recruits who are at unacceptably high risk of EHI, and must therefore be treated differently during training.

In summary, we have found that heat illness continues to be a problem during Marine training. We have identified both environmental and personal risk factors, and suggested ways that this knowledge can be used for prevention. We have also presented evidence that those who are hospitalized for heat illness may be at increased risk of mortality. Whether this is due to direct organic damage from the heat illness cannot at present be determined. We hope that the results from these studies lead to changes in training guidelines so that EHI can be effectively prevented.

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[i] The information contained herein was derived from data provided by the Office of Vital Statistics, New York City Department of Health.

[ii] The information contained herein was derived from data provided by the State of Tennessee, Department of Health, Office of Health Statistics and Research, Nashville, TN.

[iii] These data were supplied by the Health Statistics Section of the Colorado Department of Public Health and Environment, which specifically disclaims responsibility for any analyses, interpretations, or conclusions it has not provided.